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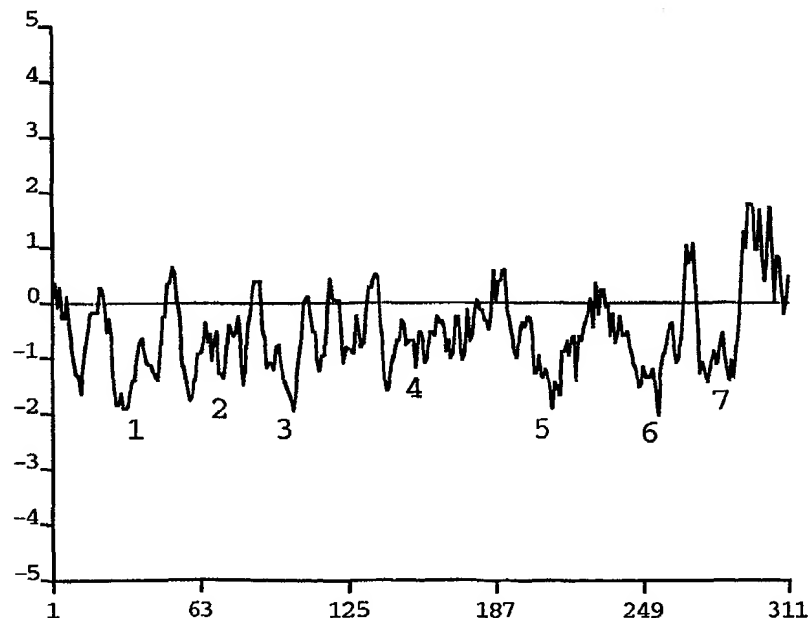
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(54) Title: **G-PROTEIN COUPLED RECEPTORS**



(57) Abstract: The invention provides human G-protein coupled receptors (GCREC) and polynucleotides which identify and encode GCREC. The invention also provides expression vectors, host, cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with aberrant expression of GCREC.

WO 01/42288 A2



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## G-PROTEIN COUPLED RECEPTORS

### TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of G-protein coupled receptors  
5 and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative,  
neurological, cardiovascular, gastrointestinal, autoimmune/inflammatory, and metabolic disorders, and  
viral infections, and in the assessment of the effects of exogenous compounds on the expression of  
nucleic acid and amino acid sequences of G-protein coupled receptors.

### 10 BACKGROUND OF THE INVENTION

Signal transduction is the general process by which cells respond to extracellular signals.  
Signal transduction across the plasma membrane begins with the binding of a signal molecule, e.g., a  
hormone, neurotransmitter, or growth factor, to a cell membrane receptor. The receptor, thus activated,  
triggers an intracellular biochemical cascade that ends with the activation of an intracellular target  
15 molecule, such as a transcription factor. This process of signal transduction regulates all types of cell  
functions including cell proliferation, differentiation, and gene transcription. The G-protein coupled  
receptors (GPCRs), encoded by one of the largest families of genes yet identified, play a central role in  
the transduction of extracellular signals across the plasma membrane. GPCRs have a proven history of  
being successful therapeutic targets.

20 GPCRs are integral membrane proteins characterized by the presence of seven hydrophobic  
transmembrane domains which together form a bundle of antiparallel alpha ( $\alpha$ ) helices. GPCRs range  
in size from under 400 to over 1000 amino acids (Strosberg, A.D. (1991) Eur. J. Biochem. 196:1-10;  
Coughlin, S.R. (1994) Curr. Opin. Cell Biol. 6:191-197). The amino-terminus of a GPCR is  
extracellular, is of variable length, and is often glycosylated. The carboxy-terminus is cytoplasmic and  
25 generally phosphorylated. Extracellular loops alternate with intracellular loops and link the  
transmembrane domains. Cysteine disulfide bridges linking the second and third extracellular loops  
may interact with agonists and antagonists. The most conserved domains of GPCRs are the  
transmembrane domains and the first two cytoplasmic loops. The transmembrane domains account, in  
part, for structural and functional features of the receptor. In most cases, the bundle of  $\alpha$  helices forms  
30 a ligand-binding pocket. The extracellular N-terminal segment, or one or more of the three extracellular  
loops, may also participate in ligand binding. Ligand binding activates the receptor by inducing a  
conformational change in intracellular portions of the receptor. In turn, the large, third intracellular  
loop of the activated receptor interacts with a heterotrimeric guanine nucleotide binding (G) protein  
complex which mediates further intracellular signaling activities, including the activation of second

messengers such as cyclic AMP (cAMP), phospholipase C, and inositol triphosphate, and the interaction of the activated GPCR with ion channel proteins. (See, e.g., Watson, S. and S. Arkininstall (1994) The G-protein Linked Receptor Facts Book, Academic Press, San Diego CA, pp. 2-6; Bolander, F.F. (1994) Molecular Endocrinology, Academic Press, San Diego CA, pp. 162-176;

- 5 Baldwin, J.M. (1994) *Curr. Opin. Cell Biol.* 6:180-190.)

GPCRs include receptors for sensory signal mediators (e.g., light and olfactory stimulatory molecules); adenosine,  $\gamma$ -aminobutyric acid (GABA), hepatocyte growth factor, melanocortins, neuropeptide Y, opioid peptides, opsins, somatostatin, tachykinins, vasoactive intestinal polypeptide family, and vasopressin; biogenic amines (e.g., dopamine, epinephrine and norepinephrine, histamine, glutamate (metabotropic effect), acetylcholine (muscarinic effect), and serotonin); chemokines; lipid mediators of inflammation (e.g., prostaglandins and prostanoids, platelet activating factor, and leukotrienes); and peptide hormones (e.g., bombesin, bradykinin, calcitonin, C5a anaphylatoxin, endothelin, follicle-stimulating hormone (FSH), gonadotropic-releasing hormone (GnRH), neurokinin, and thyrotropin-releasing hormone (TRH), and oxytocin). GPCRs which act as receptors for stimuli  
15 that have yet to be identified are known as orphan receptors.

The diversity of the GPCR family is further increased by alternative splicing. Many GPCR genes contain introns, and there are currently over 30 such receptors for which splice variants have been identified. The largest number of variations are at the protein C-terminus. N-terminal and cytoplasmic loop variants are also frequent, while variants in the extracellular loops or transmembrane domains are  
20 less common. Some receptors have more than one site at which variance can occur. The splicing variants appear to be functionally distinct, based upon observed differences in distribution, signaling, coupling, regulation, and ligand binding profiles (Kilpatrick, G.J. et al. (1999) *Trends Pharmacol. Sci.* 20:294-301).

GPCRs can be divided into three major subfamilies: the rhodopsin-like, secretin-like, and  
25 metabotropic glutamate receptor subfamilies. Members of these GPCR subfamilies share similar functions and the characteristic seven transmembrane structure, but have divergent amino acid sequences. The largest family consists of the rhodopsin-like GPCRs, which transmit diverse extracellular signals including hormones, neurotransmitters, and light. Rhodopsin is a photosensitive GPCR found in animal retinas. In vertebrates, rhodopsin molecules are embedded in membranous  
30 stacks found in photoreceptor (rod) cells. Each rhodopsin molecule responds to a photon of light by triggering a decrease in cGMP levels which leads to the closure of plasma membrane sodium channels. In this manner, a visual signal is converted to a neural impulse. Other rhodopsin-like GPCRs are directly involved in responding to neurotransmitters. These GPCRs include the receptors for adrenaline (adrenergic receptors), acetylcholine (muscarinic receptors), adenosine, galanin, and glutamate (N-



methyl-D-aspartate/NMDA receptors). (Reviewed in Watson, S. and S. Arkinstall (1994) The G-Protein Linked Receptor Facts Book, Academic Press, San Diego CA, pp. 7-9, 19-22, 32-35, 130-131, 214-216, 221-222; Habert-Ortoli, E. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9780-9783.)

The galanin receptors mediate the activity of the neuroendocrine peptide galanin, which  
5 inhibits secretion of insulin, acetylcholine, serotonin and noradrenaline, and stimulates prolactin and growth hormone release. Galanin receptors are involved in feeding disorders, pain, depression, and Alzheimer's disease (Kask, K. et al. (1997) Life Sci. 60:1523-1533). Other nervous system rhodopsin-like GPCRs include a growing family of receptors for lysophosphatidic acid and other  
10 lysophospholipids, which appear to have roles in development and neuropathology (Chun, J. et al. (1999) Cell Biochem. Biophys. 30:213-242).

The largest subfamily of GPCRs, the olfactory receptors, are also members of the rhodopsin-like GPCR family. These receptors function by transducing odorant signals. Numerous distinct olfactory receptors are required to distinguish different odors. Each olfactory sensory neuron expresses only one type of olfactory receptor, and distinct spatial zones of neurons expressing distinct receptors  
15 are found in nasal passages. For example, the RA1c receptor which was isolated from a rat brain library, has been shown to be limited in expression to very distinct regions of the brain and a defined zone of the olfactory epithelium (Raming, K. et al. (1998) Receptors Channels 6:141-151). However, the expression of olfactory-like receptors is not confined to olfactory tissues. For example, three rat genes encoding olfactory-like receptors having typical GPCR characteristics showed expression  
20 patterns not only in taste and olfactory tissue, but also in male reproductive tissue (Thomas, M.B. et al. (1996) Gene 178:1-5).

Members of the secretin-like GPCR subfamily have as their ligands peptide hormones such as secretin, calcitonin, glucagon, growth hormone-releasing hormone, parathyroid hormone, and vasoactive intestinal peptide. For example, the secretin receptor responds to secretin, a peptide  
25 hormone that stimulates the secretion of enzymes and ions in the pancreas and small intestine (Watson, supra, pp. 278-283). Secretin receptors are about 450 amino acids in length and are found in the plasma membrane of gastrointestinal cells. Binding of secretin to its receptor stimulates the production of cAMP.

Examples of secretin-like GPCRs implicated in inflammation and the immune response  
30 include the EGF module-containing, mucin-like hormone receptor (Emr1) and CD97 receptor proteins. These GPCRs are members of the recently characterized EGF-TM7 receptors subfamily. These seven transmembrane hormone receptors exist as heterodimers in vivo and contain between three and seven potential calcium-binding EGF-like motifs. CD97 is predominantly expressed in leukocytes and is markedly upregulated on activated B and T cells (McKnight, A.J. and S. Gordon  
35 (1998) J. Leukoc. Biol. 63:271-280).

The third GPCR subfamily is the metabotropic glutamate receptor family. Glutamate is the major excitatory neurotransmitter in the central nervous system. The metabotropic glutamate receptors modulate the activity of intracellular effectors, and are involved in long-term potentiation (Watson, supra, p.130). The  $\text{Ca}^{2+}$ -sensing receptor, which senses changes in the extracellular concentration of calcium ions, has a large extracellular domain including clusters of acidic amino acids which may be involved in calcium binding. The metabotropic glutamate receptor family also includes pheromone receptors, the  $\text{GABA}_B$  receptors, and the taste receptors.

Other subfamilies of GPCRs include two groups of chemoreceptor genes found in the nematodes Caenorhabditis elegans and Caenorhabditis briggsae, which are distantly related to the mammalian olfactory receptor genes. The yeast pheromone receptors STE2 and STE3, involved in the response to mating factors on the cell membrane, have their own seven-transmembrane signature, as do the cAMP receptors from the slime mold Dictyostelium discoideum, which are thought to regulate the aggregation of individual cells and control the expression of numerous developmentally-regulated genes.

GPCR mutations, which may cause loss of function or constitutive activation, have been associated with numerous human diseases (Coughlin, supra). For instance, retinitis pigmentosa may arise from mutations in the rhodopsin gene. Furthermore, somatic activating mutations in the thyrotropin receptor have been reported to cause hyperfunctioning thyroid adenomas, suggesting that certain GPCRs susceptible to constitutive activation may behave as protooncogenes (Parma, J. et al. (1993) Nature 365:649-651). GPCR receptors for the following ligands also contain mutations associated with human disease: luteinizing hormone (precocious puberty); vasopressin  $\text{V}_2$  (X-linked nephrogenic diabetes); glucagon (diabetes and hypertension); calcium (hyperparathyroidism, hypocalcuria, hypercalcemia); parathyroid hormone (short limbed dwarfism);  $\beta_3$ -adrenoceptor (obesity, non-insulin-dependent diabetes mellitus); growth hormone releasing hormone (dwarfism); and adrenocorticotropin (glucocorticoid deficiency) (Wilson, S. et al. (1998) Br. J. Pharmacol. 125:1387-1392; Stadel, J.M. et al. (1997) Trends Pharmacol. Sci. 18:430-437). GPCRs are also involved in depression, schizophrenia, sleeplessness, hypertension, anxiety, stress, renal failure, and several cardiovascular disorders (Horn, F. and G. Vriend (1998) J. Mol. Med. 76:464-468).

In addition, within the past 20 years several hundred new drugs have been recognized that are directed towards activating or inhibiting GPCRs. The therapeutic targets of these drugs span a wide range of diseases and disorders, including cardiovascular, gastrointestinal, and central nervous system disorders as well as cancer, osteoporosis and endometriosis (Wilson, supra; Stadel, supra). For example, the dopamine agonist L-dopa is used to treat Parkinson's disease, while a dopamine antagonist is used to treat schizophrenia and the early stages of Huntington's disease. Agonists and antagonists of adrenoceptors have been used for the treatment of asthma, high blood pressure, other cardiovascular

disorders, and anxiety; muscarinic agonists are used in the treatment of glaucoma and tachycardia; serotonin 5HT<sub>1D</sub> antagonists are used against migraine; and histamine H<sub>1</sub> antagonists are used against allergic and anaphylactic reactions, hay fever, itching, and motion sickness (Horn, *supra*).

Recent research suggests potential future therapeutic uses for GPCRs in the treatment of  
5 metabolic disorders including diabetes, obesity, and osteoporosis. For example, mutant V2 vasopressin receptors causing nephrogenic diabetes could be functionally rescued *in vitro* by co-expression of a C-terminal V2 receptor peptide spanning the region containing the mutations. This result suggests a possible novel strategy for disease treatment (Schöneberg, T. et al. (1996) EMBO J. 15:1283-1291). Mutations in melanocortin-4 receptor (MC4R) are implicated in human weight regulation and obesity.  
10 As with the vasopressin V2 receptor mutants, these MC4R mutants are defective in trafficking to the plasma membrane (Ho, G. and R.G. MacKenzie (1999) J. Biol. Chem. 274:35816-35822), and thus might be treated with a similar strategy. The type 1 receptor for parathyroid hormone (PTH) is a GPCR that mediates the PTH-dependent regulation of calcium homeostasis in the bloodstream. Study of PTH/receptor interactions may enable the development of novel PTH receptor ligands for the  
15 treatment of osteoporosis (Mannstadt, M. et al. (1999) Am. J. Physiol. 277:F665-F675).

The chemokine receptor group of GPCRs have potential therapeutic utility in inflammation and infectious disease. (For review, see Locati, M. and P.M. Murphy (1999) Annu. Rev. Med. 50:425-440.) Chemokines are small polypeptides that act as intracellular signals in the regulation of leukocyte trafficking, hematopoiesis, and angiogenesis. Targeted disruption of various chemokine receptors in  
20 mice indicates that these receptors play roles in pathologic inflammation and in autoimmune disorders such as multiple sclerosis. Chemokine receptors are also exploited by infectious agents, including herpesviruses and the human immunodeficiency virus (HIV-1) to facilitate infection. A truncated version of chemokine receptor CCR5, which acts as a coreceptor for infection of T-cells by HIV-1, results in resistance to AIDS, suggesting that CCR5 antagonists could be useful in preventing the  
25 development of AIDS.

The discovery of new G-protein coupled receptors and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative, neurological, cardiovascular, gastrointestinal, autoimmune/inflammatory, and metabolic disorders, and viral infections, and in the assessment of the  
30 effects of exogenous compounds on the expression of nucleic acid and amino acid sequences of G-protein coupled receptors.

## SUMMARY OF THE INVENTION

The invention features purified polypeptides, G-protein coupled receptors, referred to

collectively as "GCREC" and individually as "GCREC-1," "GCREC-2," "GCREC-3," "GCREC-4," "GCREC-5," "GCREC-6," "GCREC-7," "GCREC-8," "GCREC-9," "GCREC-10," "GCREC-11," "GCREC-12," "GCREC-13," "GCREC-14," "GCREC-15," "GCREC-16," "GCREC-17," "GCREC-18," "GCREC-19," "GCREC-20," "GCREC-21," "GCREC-22," "GCREC-23," "GCREC-24,"  
5 "GCREC-25," "GCREC-26," "GCREC-27," "GCREC-28," "GCREC-29," "GCREC-30," "GCREC-31," "GCREC-32," "GCREC-33," "GCREC-34," "GCREC-35," "GCREC-36," "GCREC-37," "GCREC-38," and "GCREC-39." In one aspect, the invention provides an isolated polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence  
10 having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-39.

15 The invention further provides an isolated polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of  
20 SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-39. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:40-78.

25 Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c)  
30 a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising an amino acid

sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

10 Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39.

The invention further provides an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

25 Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and

optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence  
5 selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or  
10 fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

The invention further provides a composition comprising an effective amount of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence  
15 selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and a pharmaceutically acceptable excipient. In one  
20 embodiment, the composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional GCREC, comprising administering to a patient in need of such treatment the composition.

The invention also provides a method for screening a compound for effectiveness as an  
25 agonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino  
30 acid sequence selected from the group consisting of SEQ ID NO:1-39. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of  
35 functional GCREC, comprising administering to a patient in need of such treatment the composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence  
5 selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a composition comprising  
10 an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional GCREC, comprising administering to a patient in need of such treatment the composition.

The invention further provides a method of screening for a compound that specifically binds  
15 to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid  
20 sequence selected from the group consisting of SEQ ID NO:1-39. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the  
25 activity of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino  
30 acid sequence selected from the group consisting of SEQ ID NO:1-39. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a change in the activity of  
35 the polypeptide in the presence of the test compound is indicative of a compound that modulates the

activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:40-78, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound; b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, ii) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, ii) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide comprises a fragment of a polynucleotide sequence selected from the group consisting of i)-v) above; c) quantifying the amount of hybridization complex; and d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

#### BRIEF DESCRIPTION OF THE FIGURES AND TABLES

Figure 1 shows the hydrophobicity plot for GCREC-1 (SEQ ID NO:1; Incyte ID number 104941CD1). The hydrophobicity plot was generated using the MacDNASIS Pro software. The positive X axis reflects amino acid position, and the negative Y axis, hydrophobicity. The numbers indicate the positions of predicted transmembrane domains.

Figure 2 shows the hydrophobicity plot for GCREC-3 (SEQ ID NO:3; Incyte ID number 3168839CD1).



Figure 3 shows the hydrophobicity plot for GCREC-4 (SEQ ID NO:4; Incyte ID number 3291235CD1).

Figure 4 shows the hydrophobicity plot for GCREC-5 (SEQ ID NO:5; Incyte ID number 7472001CD1).

5 Figure 5 shows the hydrophobicity plot for GCREC-6 (SEQ ID NO:6; Incyte ID number 7472003CD1).

Figure 6 shows the hydrophobicity plot for GCREC-7 (SEQ ID NO:7; Incyte ID number 7472004CD1).

10 Figure 7 shows the hydrophobicity plot for GCREC-19 (SEQ ID NO:19; Incyte ID number 3068234CD1).

Figure 8 shows the hydrophobicity plot for GCREC-20 (SEQ ID NO:20; Incyte ID number 5029478CD1).

Figure 9 shows the hydrophobicity plot for GCREC-21 (SEQ ID NO:21; Incyte ID number 5102576CD1).

15 Table 1 summarizes the nomenclature for the polynucleotide and polypeptide sequences of the present invention.

Table 2 shows the GenBank identification number and annotation of the nearest GenBank homolog for each polypeptide of the invention. The probability score for the match between each polypeptide and its GenBank homolog is also shown.

20 Table 3 shows structural features of each polypeptide sequence, including predicted motifs and domains, along with the methods, algorithms, and searchable databases used for analysis of each polypeptide.

Table 4 lists the cDNA and genomic DNA fragments which were used to assemble each polynucleotide sequence, along with selected fragments of the polynucleotide sequences.

25 Table 5 shows the representative cDNA library for each polynucleotide of the invention.

Table 6 provides an appendix which describes the tissues and vectors used for construction of the cDNA libraries shown in Table 5.

Table 7 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

30

## DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing

particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a  
5 reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although  
10 any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is  
15 not entitled to antedate such disclosure by virtue of prior invention.

#### DEFINITIONS

"GCREC" refers to the amino acid sequences of substantially purified GCREC obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

20 The term "agonist" refers to a molecule which intensifies or mimics the biological activity of GCREC. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of GCREC either by directly interacting with GCREC or by acting on components of the biological pathway in which GCREC participates.

An "allelic variant" is an alternative form of the gene encoding GCREC. Allelic variants may  
25 result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in  
30 a given sequence.

"Altered" nucleic acid sequences encoding GCREC include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as GCREC or a polypeptide with at least one functional characteristic of GCREC. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of

the polynucleotide encoding GCREC, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding GCREC. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent GCREC.

- 5 Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of GCREC is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity
- 10 values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic

15 molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known

20 in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of GCREC. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of GCREC either by directly interacting with GCREC or by acting on components of the biological pathway in which

25 GCREC participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')<sub>2</sub>, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind GCREC polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or

30 oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

35 The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that

makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to  
5 elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified  
10 sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or  
15 translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic" refers to the capability of the natural, recombinant, or synthetic GCREC, or of any oligopeptide thereof,  
20 to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement, 3'-TCA-5'.

25 A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding GCREC or fragments of GCREC may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be  
30 associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (Applied Biosystems,

Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
	Ala	Gly, Ser
	Arg	His, Lys
	Asn	Asp, Gln, His
15	Asp	Asn, Glu
	Cys	Ala, Ser
	Gln	Asn, Glu, His
	Glu	Asp, Gln, His
	Gly	Ala
20	His	Asn, Arg, Gln, Glu
	Ile	Leu, Val
	Leu	Ile, Val
	Lys	Arg, Gln, Glu
	Met	Leu, Ile
25	Phe	His, Met, Leu, Trp, Tyr
	Ser	Cys, Thr
	Thr	Ser, Val
	Trp	Phe, Tyr
	Tyr	His, Phe, Trp
30	Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. Chemical modifications of a polynucleotide can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified

by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

5 A "fragment" is a unique portion of GCREC or the polynucleotide encoding GCREC which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least  
10 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50%) of a polypeptide as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported  
15 by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:40-78 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:40-78, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:40-78 is useful, for  
20 example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:40-78 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:40-78 and the region of SEQ ID NO:40-78 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-39 is encoded by a fragment of SEQ ID NO:40-78. A fragment  
25 of SEQ ID NO:1-39 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-39. For example, a fragment of SEQ ID NO:1-39 is useful as an immunogenic peptide

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The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore  
5 achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G.  
10 and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequences.

15 Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis  
20 programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bi2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST  
25 programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

*Matrix: BLOSUM62*

*Reward for match: 1*

30 *Penalty for mismatch: -2*

*Open Gap: 5 and Extension Gap: 2 penalties*

*Gap x drop-off: 50*

*Expect: 10*

*Word Size: 11*

*Filter: on*

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

*Matrix: BLOSUM62*

*Open Gap: 11 and Extension Gap: 1 penalties*

*Gap x drop-off: 50*

*Expect: 10*

*Word Size: 3*

*Filter: on*



Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150  
5 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

“Human artificial chromosomes” (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size and which contain all of the elements required for  
10 chromosome replication, segregation and maintenance.

The term “humanized antibody” refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

“Hybridization” refers to the process by which a polynucleotide strand anneals with a  
15 complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the “washing” step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e.,  
20 binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v)  
25 SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point ( $T_m$ ) for the specific sequence at a defined ionic strength and pH. The  $T_m$  is the temperature (under defined ionic strength and pH) at which 50% of the  
30 target sequence hybridizes to a perfectly matched probe. An equation for calculating  $T_m$  and conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention

include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C<sub>0</sub>t or R<sub>0</sub>t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of GCREC which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of GCREC which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides, polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

The term "modulate" refers to a change in the activity of GCREC. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of GCREC.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide,

polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Post-translational modification" of an GCREC may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of GCREC.

"Probe" refers to nucleic acid sequences encoding GCREC, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al. (1987) Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al. (1990) PCR

Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

5 Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU  
10 primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer  
15 binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that  
20 hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary  
25 polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the  
30 artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

5 A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription, translation, or RNA stability.

"Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid, amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, 10 chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose 15 instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing GCREC, nucleic acids encoding GCREC, or fragments thereof may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

20 The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope 25 A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which 30 they are naturally associated.

A "substitution" refers to the replacement of one or more amino acid residues or nucleotides by different amino acid residues or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers,

microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

A "transcript image" refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

5        "Transformation" describes a process by which exogenous DNA is introduced into a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection, 10 electroporation, heat shock, lipofection, and particle bombardment. The term "transformed cells" includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "transgenic organism," as used herein, is any organism, including but not limited to 15 animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in 20 vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, plants and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention 25 into such organisms are widely known and provided in references such as Sambrook et al. (1989), supra.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) 30 set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides 35 due to alternative splicing of exons during mRNA processing. The corresponding polypeptide may

possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides will generally have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

## 15 THE INVENTION

The invention is based on the discovery of new human G-protein coupled receptors (GCREC), the polynucleotides encoding GCREC, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, neurological, cardiovascular, gastrointestinal, autoimmune/inflammatory, and metabolic disorders, and viral infections.

Table 1 summarizes the nomenclature for the polynucleotide and polypeptide sequences of the invention. Each polynucleotide and its corresponding polypeptide are correlated to a single Incyte project identification number (Incyte Project ID). Each polypeptide sequence is denoted by both a polypeptide sequence identification number (Polypeptide SEQ ID NO:) and an Incyte polypeptide sequence number (Incyte Polypeptide ID) as shown. Each polynucleotide sequence is denoted by both a polynucleotide sequence identification number (Polynucleotide SEQ ID NO:) and an Incyte polynucleotide consensus sequence number (Incyte Polynucleotide ID) as shown.

Table 2 shows sequences with homology to the polypeptides of the invention as identified by BLAST analysis against the GenBank protein (genpept) database. Columns 1 and 2 show the polypeptide sequence identification number (Polypeptide SEQ ID NO:) and the corresponding Incyte polypeptide sequence number (Incyte Polypeptide ID) for each polypeptide of the invention. Column 3 shows the GenBank identification number (Genbank ID NO:) of the nearest GenBank homolog. Column 4 shows the probability score for the match between each polypeptide and its GenBank homolog. Column 5 shows the annotation of the GenBank homolog along with relevant citations where applicable, all of which are expressly incorporated by reference herein.

Table 3 shows various structural features of each of the polypeptides of the invention. Columns

1 and 2 show the polypeptide sequence identification number (SEQ ID NO:) and the corresponding Incyte polypeptide sequence number (Incyte Polypeptide ID) for each polypeptide of the invention. Column 3 shows the number of amino acid residues in each polypeptide. Column 4 shows potential phosphorylation sites, and column 5 shows potential glycosylation sites, as determined by the MOTIFS program of the GCG sequence analysis software package (Genetics Computer Group, Madison WI). Column 6 shows amino acid residues comprising signature sequences, domains, and motifs. Column 7 shows analytical methods for protein structure/function analysis and in some cases, searchable databases to which the analytical methods were applied.

As shown in Table 4, the polynucleotide sequences of the present invention were assembled using cDNA sequences or coding (exon) sequences derived from genomic DNA, or any combination of these two types of sequences. Columns 1 and 2 list the polynucleotide sequence identification number (Polynucleotide SEQ ID NO:) and the corresponding Incyte polynucleotide consensus sequence number (Incyte Polynucleotide ID) for each polynucleotide of the invention. Column 3 shows the length of each polynucleotide sequence in basepairs. Column 4 lists fragments of the polynucleotide sequences which are useful, for example, in hybridization or amplification technologies that identify SEQ ID NO:40-78 or that distinguish between SEQ ID NO:40-78 and related polynucleotide sequences. Column 5 shows identification numbers corresponding to cDNA sequences, coding sequences (exons) predicted from genomic DNA, and/or sequence assemblages comprised of both cDNA and genomic DNA. These sequences were used to assemble the polynucleotide sequences of the invention. Columns 6 and 7 of Table 4 show the nucleotide start (5') and stop (3') positions of the cDNA and genomic sequences in column 5 relative to their respective sequences.

The identification numbers in Column 5 of Table 4 may refer specifically, for example, to Incyte cDNAs along with their corresponding cDNA libraries. For example, 927003T6 is the identification number of an Incyte cDNA sequence, and BRAINOT04 is the cDNA library from which it is derived. Incyte cDNAs for which cDNA libraries are not indicated were derived from pooled cDNA libraries (e.g., 70489898V1). Alternatively, the identification numbers in column 5 may refer to GenBank cDNAs or ESTs (e.g., g835247) which contributed to the assembly of the polynucleotide sequences. Alternatively, the identification numbers in column 5 may refer to coding regions predicted by Genscan analysis of genomic DNA. For example, g4190944.v113.gs\_10.edit is the identification number of a Genscan-predicted coding sequence, with g4190944 being the GenBank identification number of the sequence to which Genscan was applied. The Genscan-predicted coding sequences may have been edited prior to assembly. (See Example IV.) Alternatively, the identification numbers in column 5 may refer to assemblages of both cDNA and Genscan-predicted exons brought together by an "exon stitching" algorithm. (See Example V.) Alternatively, the identification numbers in column 5



may refer to assemblages of both cDNA and Genscan-predicted exons brought together by an "exon-stretching" algorithm. (See Example V.) In some cases, Incyte cDNA coverage redundant with the sequence coverage shown in column 5 was obtained to confirm the final consensus polynucleotide sequence, but the relevant Incyte cDNA identification numbers are not shown.

5        Table 5 shows the representative cDNA libraries for those polynucleotide sequences which were assembled using Incyte cDNA sequences. The representative cDNA library is the Incyte cDNA library which is most frequently represented by the Incyte cDNA sequences which were used to assemble and confirm the above polynucleotide sequences. The tissues and vectors which were used to construct the cDNA libraries shown in Table 5 are described in Table 6.

10        The invention also encompasses GCREC variants. A preferred GCREC variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the GCREC amino acid sequence, and which contains at least one functional or structural characteristic of GCREC.

15        The invention also encompasses polynucleotides which encode GCREC. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:40-78, which encodes GCREC. The polynucleotide sequences of SEQ ID NO:40-78, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

20        The invention also encompasses a variant of a polynucleotide sequence encoding GCREC. In particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding GCREC. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:40-78 which has at  
25        least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:40-78. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of GCREC.

30        It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding GCREC, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally

occurring GCREC, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode GCREC and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring GCREC under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding GCREC or  
5 its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding GCREC and its derivatives without altering the encoded amino acid sequences  
10 include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode GCREC and GCREC derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems  
15 using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding GCREC or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:40-78 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and  
20 S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.* 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of  
25 DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Applied Biosystems), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV),  
30 PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Applied Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Applied Biosystems), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols

in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding GCREC may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 primer analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Applied Biosystems), and the entire

process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which  
5 encode GCREC may be cloned in recombinant DNA molecules that direct expression of GCREC, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express GCREC.

The nucleotide sequences of the present invention can be engineered using methods generally  
10 known in the art in order to alter GCREC-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites,  
15 alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 17:259-264; and Cramer, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or  
20 improve the biological properties of GCREC, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired properties. These preferred variants may then be pooled and further subjected to recursive rounds of  
25 DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby  
30 maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

In another embodiment, sequences encoding GCREC may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.) Alternatively,  
35 GCREC itself or a fragment thereof may be synthesized using chemical methods. For example, peptide

synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY, pp.55-60; and Roberge, J.Y. et al. (1995) *Science* 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Applied Biosystems). Additionally, the amino acid sequence of GCREC, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) *Methods Enzymol.* 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, *supra*, pp. 28-53.)

In order to express a biologically active GCREC, the nucleotide sequences encoding GCREC or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding GCREC. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding GCREC. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding GCREC and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding GCREC and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding GCREC. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus);

5 plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509; Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu, N. (1987) EMBO

10 J. 6:307-311; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.) Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di

15 Nicola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al. (1993) Proc. Natl. Acad. Sci. USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al. (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M. and N. Somia (1997) Nature 389:239-242.) The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending

20 upon the use intended for polynucleotide sequences encoding GCREC. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding GCREC can be achieved using a multifunctional *E. coli* vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding GCREC into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed

25 bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of GCREC are needed, e.g. for the production of antibodies, vectors which direct high level expression of GCREC may be used. For example, vectors containing

30 the strong, inducible SP6 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of GCREC. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast *Saccharomyces cerevisiae* or *Pichia pastoris*. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration

35 of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra;

Bitter, G.A. et al. (1987) *Methods Enzymol.* 153:516-544; and Scorer, C.A. et al. (1994) *Bio/Technology* 12:181-184.)

Plant systems may also be used for expression of GCREC. Transcription of sequences encoding GCREC may be driven by viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding GCREC may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses GCREC in host cells. (See, e.g., Logan, J. and T. Shenk (1984) *Proc. Natl. Acad. Sci. USA* 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) *Nat. Genet.* 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of GCREC in cell lines is preferred. For example, sequences encoding GCREC can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase

genes, for use in *tk<sup>-</sup>* and *ap<sup>r</sup>* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to

5 chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech),  $\beta$

10 glucuronidase and its substrate  $\beta$ -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is

15 also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding GCREC is inserted within a marker gene sequence, transformed cells containing sequences encoding GCREC can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding GCREC under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates

20 expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding GCREC and that express GCREC may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or

25 chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of GCREC using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal

30 antibodies reactive to two non-interfering epitopes on GCREC is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)



A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding GCREC include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide.

- 5 Alternatively, the sequences encoding GCREC, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega  
10 (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

- Host cells transformed with nucleotide sequences encoding GCREC may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein  
15 produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode GCREC may be designed to contain signal sequences which direct secretion of GCREC through a prokaryotic or eukaryotic cell membrane.

- In addition, a host cell strain may be chosen for its ability to modulate expression of the  
20 inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities  
25 (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

- In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding GCREC may be ligated to a heterologous sequence resulting in translation of a  
30 fusion protein in any of the aforementioned host systems. For example, a chimeric GCREC protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of GCREC activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose

binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the GCREC encoding sequence and the heterologous protein sequence, so that GCREC may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled GCREC may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, <sup>35</sup>S-methionine.

GCREC of the present invention or fragments thereof may be used to screen for compounds that specifically bind to GCREC. At least one and up to a plurality of test compounds may be screened for specific binding to GCREC. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

In one embodiment, the compound thus identified is closely related to the natural ligand of GCREC, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, e.g., Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which GCREC binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the compound can be rationally designed using known techniques. In one embodiment, screening for these compounds involves producing appropriate cells which express GCREC, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing GCREC or cell membrane fractions which contain GCREC are then contacted with a test compound and binding, stimulation, or inhibition of activity of either GCREC or the compound is analyzed.

An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with GCREC, either in solution or affixed to a solid support, and detecting the binding of GCREC to the compound.

Alternatively, the assay may detect or measure binding of a test compound in the presence of a

labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

GCREC of the present invention or fragments thereof may be used to screen for compounds  
5 that modulate the activity of GCREC. Such compounds may include agonists, antagonists, or partial or inverse agonists. In one embodiment, an assay is performed under conditions permissive for GCREC activity, wherein GCREC is combined with at least one test compound, and the activity of GCREC in the presence of a test compound is compared with the activity of GCREC in the absence of the test compound. A change in the activity of GCREC in the presence of the test compound is  
10 indicative of a compound that modulates the activity of GCREC. Alternatively, a test compound is combined with an *in vitro* or cell-free system comprising GCREC under conditions suitable for GCREC activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of GCREC may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

15 In another embodiment, polynucleotides encoding GCREC or their mammalian homologs may be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent Number 5,175,383 and U.S. Patent Number 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo  
20 and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D.  
25 (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

30 Polynucleotides encoding GCREC may also be manipulated *in vitro* in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

35 Polynucleotides encoding GCREC can also be used to create "knockin" humanized animals

(pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding GCREC is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress GCREC, e.g., by secreting GCREC in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) *Biotechnol. Annu. Rev.* 4:55-74).

### THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of GCREC and G-protein coupled receptors. In addition, the expression of GCREC is closely associated with cancerous, neurological, gastrointestinal, and lung tissue. Therefore, GCREC appears to play a role in cell proliferative, neurological, cardiovascular, gastrointestinal, autoimmune/inflammatory, and metabolic disorders, and viral infections. In the treatment of disorders associated with increased GCREC expression or activity, it is desirable to decrease the expression or activity of GCREC. In the treatment of disorders associated with decreased GCREC expression or activity, it is desirable to increase the expression or activity of GCREC.

Therefore, in one embodiment, GCREC or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GCREC. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental

retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia

5 gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, Tourette's disorder, progressive supranuclear palsy, corticobasal degeneration, and familial frontotemporal dementia; a cardiovascular

10 disorder such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, vascular tumors, complications of thrombolysis, balloon angioplasty, vascular replacement, and coronary artery bypass graft surgery, congestive heart failure, ischemic heart disease, angina pectoris, myocardial infarction, hypertensive heart disease, degenerative valvular heart disease, calcific aortic valve stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse,

15 rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, congenital heart disease, and complications of cardiac transplantation; a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric

20 carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome,

25 colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, alpha<sub>1</sub>-antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis,

30 hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hepatic tumors including nodular hyperplasias, adenomas, and carcinomas; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune

35 hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal

dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel  
5 syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal,  
10 parasitic, protozoal, and helminthic infections, and trauma; a metabolic disorder such as diabetes, obesity, and osteoporosis; and an infection by a viral agent classified as adenovirus, arenavirus, bunyavirus, calicivirus, coronavirus, filovirus, hepadnavirus, herpesvirus, flavivirus, orthomyxovirus, parvovirus, papovavirus, paramyxovirus, picornavirus, poxvirus, reovirus, retrovirus, rhabdovirus, and togavirus.

15 In another embodiment, a vector capable of expressing GCREC or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GCREC including, but not limited to, those described above.

In a further embodiment, a composition comprising a substantially purified GCREC in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a  
20 disorder associated with decreased expression or activity of GCREC including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of GCREC may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GCREC including, but not limited to, those listed above.

25 In a further embodiment, an antagonist of GCREC may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of GCREC. Examples of such disorders include, but are not limited to, those cell proliferative, neurological, cardiovascular, gastrointestinal, autoimmune/inflammatory, and metabolic disorders, and viral infections, described above. In one aspect, an antibody which specifically binds GCREC may be used directly as an  
30 antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express GCREC.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding GCREC may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of GCREC including, but not limited to, those described above.

35 In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary

sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of GCREC may be produced using methods which are generally known in the art. In particular, purified GCREC may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind GCREC. Antibodies to GCREC may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with GCREC or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to GCREC have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of GCREC amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to GCREC may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate

antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce GCREC-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for GCREC may also be generated. For example, such fragments include, but are not limited to,  $F(ab')_2$  fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the  $F(ab')_2$  fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between GCREC and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering GCREC epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for GCREC. Affinity is expressed as an association constant,  $K_a$ , which is defined as the molar concentration of GCREC-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The  $K_a$  determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple GCREC epitopes, represents the average affinity, or avidity, of the antibodies for GCREC. The  $K_a$  determined for a preparation of monoclonal antibodies, which are monospecific for a particular GCREC epitope, represents a true measure of affinity. High-affinity antibody preparations with  $K_a$  ranging from about  $10^9$  to  $10^{12}$  L/mole are preferred for use in immunoassays in which the GCREC-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with  $K_a$



ranging from about  $10^6$  to  $10^7$  L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of GCREC, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of GCREC-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding GCREC, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding GCREC. Such technology is well known in the art, and antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding GCREC. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) *J. Allergy Clin. Immunol.* 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) *Blood* 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) *Pharmacol. Ther.* 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) *Br. Med. Bull.* 51(1):217-225; Boado, R.J. et al. (1998) *J. Pharm. Sci.* 87(11):1308-1315; and Morris, M.C. et al. (1997) *Nucleic Acids Res.* 25(14):2730-2736.)

In another embodiment of the invention, polynucleotides encoding GCREC may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) *Science* 288:669-672), severe combined

immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475), cystic fibrosis (Zabner, J. et al. (1993) Cell 75:207-216; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), thalassamias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) Science 270:404-410; Verma, I.M. and N. Somia (1997) Nature 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA. 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in GCREC expression or regulation causes disease, the expression of GCREC from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in GCREC are treated by constructing mammalian expression vectors encoding GCREC and introducing these vectors by mechanical means into GCREC-deficient cells. Mechanical transfer technologies for use with cells *in vivo* or *ex vitro* include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev. Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and H. Récipon (1998) Curr. Opin. Biotechnol. 9:445-450).

Expression vectors that may be effective for the expression of GCREC include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). GCREC may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or  $\beta$ -actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. U.S.A. 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V.

and Blau, H.M. supra), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding GCREC from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) *Virology* 52:456-467), or by electroporation (Neumann, E. et al. (1982) *EMBO J.* 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to GCREC expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding GCREC under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) *Proc. Natl. Acad. Sci. U.S.A.* 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) *J. Virol.* 61:1647-1650; Bender, M.A. et al. (1987) *J. Virol.* 61:1639-1646; Adam, M.A. and A.D. Miller (1988) *J. Virol.* 62:3802-3806; Dull, T. et al. (1998) *J. Virol.* 72:8463-8471; Zufferey, R. et al. (1998) *J. Virol.* 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference.

Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4<sup>+</sup> T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) *J. Virol.* 71:7020-7029; Bauer, G. et al. (1997) *Blood* 89:2259-2267; Bonyhadi, M.L. (1997) *J. Virol.* 71:4707-4716; Ranga, U. et al. (1998) *Proc. Natl. Acad. Sci. U.S.A.* 95:1201-1206; Su, L. (1997) *Blood* 89:2283-2290).

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding GCREC to cells which have one or more genetic abnormalities with respect to the expression of GCREC. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas

(Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annu. Rev. Nutr. 19:511-544 and Verma, I.M. and N. Somia (1997) Nature 389:239-242, both

5 incorporated by reference herein.

In another alternative, a herpes-based, gene therapy delivery system is used to deliver polynucleotides encoding GCREC to target cells which have one or more genetic abnormalities with respect to the expression of GCREC. The use of herpes simplex virus (HSV)-based vectors may be especially valuable for introducing GCREC to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) Exp. Eye Res. 169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) J. Virol. 73:519-532 and Xu, H. et al. (1994) Dev. Biol. 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus sequences, the generation of recombinant virus following the transfection of multiple plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

25 In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to deliver polynucleotides encoding GCREC to target cells. The biology of the prototypic alphavirus, Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on the SFV genome (Garoff, H. and K.-J. Li (1998) Curr. Opin. Biotechnol. 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease and polymerase). Similarly, inserting the coding sequence for GCREC into the alphavirus genome in place of the capsid-coding region results in the production of a large number of GCREC-coding RNAs and the synthesis of high levels of GCREC in vector transduced cells. While alphavirus

infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of GCREC into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding GCREC.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding GCREC. Such DNA sequences may be incorporated into a wide variety of vectors with

suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible  
5 modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine,  
10 guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding GCREC. Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming  
15 oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-macromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased GCREC expression or activity, a compound which specifically inhibits expression of the  
20 polynucleotide encoding GCREC may be therapeutically useful, and in the treatment of disorders associated with decreased GCREC expression or activity, a compound which specifically promotes expression of the polynucleotide encoding GCREC may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in altering expression of a specific polynucleotide. A test compound may be obtained by any method  
25 commonly known in the art, including chemical modification of a compound known to be effective in altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a library of chemical compounds created combinatorially or randomly. A sample comprising a  
30 polynucleotide encoding GCREC is exposed to at least one test compound thus obtained. The sample may comprise, for example, an intact or permeabilized cell, or an *in vitro* cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding GCREC are assayed by any method commonly known in the art. Typically, the expression of a specific nucleotide is detected by hybridization with a probe having a nucleotide sequence complementary to the sequence  
35 of the polynucleotide encoding GCREC. The amount of hybridization may be quantified, thus

forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of the polynucleotide. A screen for a compound effective in altering expression of a specific  
5 polynucleotide can be carried out, for example, using a Schizosaccharomyces pombe gene expression system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Arndt, G.M. et al. (2000) Nucleic Acids Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide  
10 nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruce, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruce, T.W. et al. (2000) U.S. Patent No. 6,022,691).

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken  
15 from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such  
20 therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various  
25 formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such compositions may consist of GCREC, antibodies to GCREC, and mimetics, agonists, antagonists, or inhibitors of GCREC.

The compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal,  
30 intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

Compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting  
35 formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins),

recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton. J.S. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

5        Compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

      Specialized forms of compositions may be prepared for direct intracellular delivery of macromolecules comprising GCREC or fragments thereof. For example, liposome preparations  
10        containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, GCREC or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

15        For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

20        A therapeutically effective dose refers to that amount of active ingredient, for example GCREC or fragments thereof, antibodies of GCREC, and agonists, antagonists or inhibitors of GCREC, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population) or LD<sub>50</sub> (the dose  
25        lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD<sub>50</sub>/ED<sub>50</sub> ratio. Compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED<sub>50</sub> with little or no toxicity.  
30        The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

      The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity



of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

- 5        Normal dosage amounts may vary from about 0.1  $\mu\text{g}$  to 100,000  $\mu\text{g}$ , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells,  
10    conditions, locations, etc.

### DIAGNOSTICS

- In another embodiment, antibodies which specifically bind GCREC may be used for the diagnosis of disorders characterized by expression of GCREC, or in assays to monitor patients being treated with GCREC or agonists, antagonists, or inhibitors of GCREC. Antibodies useful for  
15    diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for GCREC include methods which utilize the antibody and a label to detect GCREC in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may  
20    be used.

- A variety of protocols for measuring GCREC, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of GCREC expression. Normal or standard values for GCREC expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibodies to GCREC  
25    under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of GCREC expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

- In another embodiment of the invention, the polynucleotides encoding GCREC may be used for  
30    diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of GCREC may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of GCREC, and to monitor regulation of GCREC levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding GCRC or closely related molecules may be used to identify nucleic acid sequences which encode GCRC. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding GCRC, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the GCRC encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:40-78 or from genomic sequences including promoters, enhancers, and introns of the GCRC gene.

Means for producing specific hybridization probes for DNAs encoding GCRC include the cloning of polynucleotide sequences encoding GCRC or GCRC derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as  $^{32}\text{P}$  or  $^{35}\text{S}$ , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding GCRC may be used for the diagnosis of disorders associated with expression of GCRC. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the

nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders,

5 peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, Tourette's disorder, progressive supranuclear palsy, corticobasal degeneration, and familial

10 frontotemporal dementia; a cardiovascular disorder such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, vascular tumors, complications of thrombolysis, balloon angioplasty, vascular replacement, and coronary artery bypass graft surgery, congestive heart failure, ischemic heart disease, angina pectoris, myocardial infarction, hypertensive heart disease,

15 degenerative valvular heart disease, calcific aortic valve stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, congenital heart disease, and complications of cardiac transplantation; a gastrointestinal

20 disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis,

25 passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease,  $\alpha_1$ -

30 antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hepatic tumors including nodular hyperplasias, adenomas, and carcinomas; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's

35 disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia,

asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a metabolic disorder such as diabetes, obesity, and osteoporosis; and an infection by a viral agent classified as adenovirus, arenavirus, bunyavirus, calicivirus, coronavirus, filovirus, hepadnavirus, herpesvirus, flavivirus, orthomyxovirus, parvovirus, papovavirus, paramyxovirus, picornavirus, poxvirus, reovirus, retrovirus, rhabdovirus, and togavirus. The polynucleotide sequences encoding GCREC may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered GCREC expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding GCREC may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding GCREC may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding GCREC in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of GCREC, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding GCREC, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified

polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated,  
5 hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or  
10 overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

15 Additional diagnostic uses for oligonucleotides designed from the sequences encoding GCREC may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding GCREC, or a fragment of a polynucleotide complementary to the polynucleotide encoding GCREC, and will be employed under optimized conditions for identification of a specific gene or condition.  
20 Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding GCREC may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease  
25 in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding GCREC are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary  
30 and tertiary structures of PCR products in single-stranded form, and these differences are detectable using gel electrophoresis in non-denaturing gels. In fSSCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed *in silico* SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual

overlapping DNA fragments which assemble into a common consensus sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of GCREC include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described below. The microarray may also be used to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the activities of therapeutic agents in the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, GCREC, fragments of GCREC, or antibodies specific for GCREC may be used as elements on a microarray. The microarray may be used to monitor or measure protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

A particular embodiment relates to the use of the polynucleotides of the present invention to generate a transcript image of a tissue or cell type. A transcript image represents the global pattern of gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by quantifying the number of expressed genes and their relative abundance under given conditions and at a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Number 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by hybridizing the polynucleotides of the present invention or their complements to the totality of transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the

hybridization takes place in high-throughput format, wherein the polynucleotides of the present invention or their complements comprise a subset of a plurality of elements on a microarray. The resultant transcript image would provide a profile of gene activity.

Transcript images may be generated using transcripts isolated from tissues, cell lines, biopsies, or other biological samples. The transcript image may thus reflect gene expression in vivo, as in the case of a tissue or biopsy sample, or in vitro, as in the case of a cell line.

Transcript images which profile the expression of the polynucleotides of the present invention may also be used in conjunction with in vitro model systems and preclinical evaluation of pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental compounds. All compounds induce characteristic gene expression patterns, frequently termed molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and toxicity (Nuwaysir, E.F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N.L. Anderson (2000) Toxicol. Lett. 112-113:467-471, expressly incorporated by reference herein). If a test compound has a signature similar to that of a compound with known toxicity, it is likely to share those toxic properties. These fingerprints or signatures are most useful and refined when they contain expression information from a large number of genes and gene families. Ideally, a genome-wide measurement of expression provides the highest quality signature. Even genes whose expression is not altered by any tested compounds are important as well, as the levels of expression of these genes are used to normalize the rest of the expression data. The normalization procedure is useful for comparison of expression data after treatment with different compounds. While the assignment of gene function to elements of a toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not necessary for the statistical matching of signatures which leads to prediction of toxicity. (See, for example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released February 29, 2000, available at <http://www.niehs.nih.gov/oc/news/toxchip.htm>.) Therefore, it is important and desirable in toxicological screening using toxicant signatures to include all expressed gene sequences.

In one embodiment, the toxicity of a test compound is assessed by treating a biological sample containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated biological sample are hybridized with one or more probes specific to the polynucleotides of the present invention, so that transcript levels corresponding to the polynucleotides of the present invention may be quantified. The transcript levels in the treated biological sample are compared with levels in an untreated biological sample. Differences in the transcript levels between the two samples are indicative of a toxic response caused by the test compound in the treated sample.

Another particular embodiment relates to the use of the polypeptide sequences of the present invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global

pattern of protein expression in a particular tissue or cell type. Each protein component of a proteome can be subjected individually to further analysis. Proteome expression patterns, or profiles, are analyzed by quantifying the number of expressed proteins and their relative abundance under given conditions and at a given time. A profile of a cell's proteome may thus be generated by separating and  
5 analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the separation is achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separated by isoelectric focusing in the first dimension, and then according to molecular weight by sodium dodecyl sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, *supra*). The proteins are visualized in the gel as discrete and uniquely positioned spots, typically by staining the gel with an agent  
10 such as Coomassie Blue or silver or fluorescent stains. The optical density of each protein spot is generally proportional to the level of the protein in the sample. The optical densities of equivalently positioned protein spots from different samples, for example, from biological samples either treated or untreated with a test compound or therapeutic agent, are compared to identify any changes in protein spot density related to the treatment. The proteins in the spots are partially sequenced using, for  
15 example, standard methods employing chemical or enzymatic cleavage followed by mass spectrometry. The identity of the protein in a spot may be determined by comparing its partial sequence, preferably of at least 5 contiguous amino acid residues, to the polypeptide sequences of the present invention. In some cases, further sequence data may be obtained for definitive protein identification.

A proteomic profile may also be generated using antibodies specific for GCREC to quantify the  
20 levels of GCREC expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lucking, A. et al. (1999) *Anal. Biochem.* 270:103-111; Mendoz, L.G. et al. (1999) *Biotechniques* 27:778-788). Detection may be performed by a variety of methods known in the art, for example, by reacting the proteins in the sample with a thiol- or amino-  
25 reactive fluorescent compound and detecting the amount of fluorescence bound at each array element.

Toxicant signatures at the proteome level are also useful for toxicological screening, and should be analyzed in parallel with toxicant signatures at the transcript level. There is a poor correlation between transcript and protein abundances for some proteins in some tissues (Anderson, N.L. and J. Seilhamer (1997) *Electrophoresis* 18:533-537), so proteome toxicant signatures may be useful in the  
30 analysis of compounds which do not significantly affect the transcript image, but which alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such cases.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins that are expressed in the treated biological



sample are separated so that the amount of each protein can be quantified. The amount of each protein is compared to the amount of the corresponding protein in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample. Individual proteins are identified by sequencing the amino acid residues of the individual proteins and comparing these partial sequences to the polypeptides of the present invention.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins from the biological sample are incubated with antibodies specific to the polypeptides of the present invention. The amount of protein recognized by the antibodies is quantified. The amount of protein in the treated biological sample is compared with the amount in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

In another embodiment of the invention, nucleic acid sequences encoding GCREC may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, for example, Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

Fluorescent *in situ* hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, *supra*, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM)

World Wide Web site. Correlation between the location of the gene encoding GCREC on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) *Nature* 336:577-580.) The nucleotide sequence of the instant invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, GCREC, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between GCREC and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with GCREC, or fragments thereof, and washed. Bound GCREC is then detected by methods well known in the art. Purified GCREC can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding GCREC specifically compete with a test compound for binding GCREC. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with GCREC.

In additional embodiments, the nucleotide sequences which encode GCREC may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such

properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications and publications, mentioned above and below, in particular U.S. Ser. No. 60/172,852, U.S. Ser. No. 60/171,732, U.S. Ser. No. 60/176,148, and U.S. Ser. No. 60/177,331, are expressly incorporated by reference herein.

## EXAMPLES

### I. Construction of cDNA Libraries

Incyte cDNAs were derived from cDNA libraries described in the LIFESEQ GOLD database (Incyte Genomics, Palo Alto CA) and shown in Table 4, column 5. The Incyte cDNA shown for SEQ ID NO:40 was derived from a cDNA library constructed from bone marrow tissue. The Incyte cDNAs shown for SEQ ID NO:41 were derived from cDNA libraries constructed from small intestine, including tissues associated with Crohn's disease, from large intestine, and from brain tissues. The Incyte cDNAs shown for SEQ ID NO:42 were derived from cDNA libraries constructed from prostate tumor, small intestine, breast, and epidermal tissues. The Incyte cDNAs shown for SEQ ID NO:43 were derived cDNA libraries constructed from soft tissue tumor, fetal rib, and brain tissue associated with Huntington's disease. The Incyte cDNAs shown for SEQ ID NO:57 were derived from cDNA libraries constructed from lymphocytes and mast cells, and from breast, uterine, prostate, adrenal gland, spinal cord, tibial muscle, lung, esophagus, small intestine, and colon tissues. The Incyte cDNAs shown for SEQ ID NO:58 were derived from cDNA libraries constructed from a fallopian tube tumor, uterine endometrium, and bronchial tissue. The Incyte cDNAs shown for SEQ ID NO:59 were derived from cDNA libraries constructed from colon tissues, including cecal tumor tissue, as well as from pancreatic tumor, pituitary gland, and brain tissues. The Incyte cDNAs shown for SEQ ID NO:60 were derived from cDNA libraries constructed from brain, including brain tumor tissue and tissues associated with Huntington's disease, and from prostate tumor, cervical adenocarcinoma, breast, small intestine, and bladder tissues. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA

purity. In some cases, RNA was treated with DNase. For most libraries, poly(A)+ RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSORT1 plasmid (Life Technologies), PCDNA2.1 plasmid (Invitrogen, Carlsbad CA), or pINCY (Incyte Genomics, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 $\alpha$ , DH10B, or ElectroMAX DH10B from Life Technologies.

## II. Isolation of cDNA Clones

Plasmids obtained as described in Example I were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

## III. Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows. Sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Applied Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the  
5 MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI  
10 PRISM 373 or 377 sequencing system (Applied Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VIII.

15 The polynucleotide sequences derived from Incyte cDNAs were validated by removing vector, linker, and poly(A) sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The Incyte cDNA sequences or translations thereof were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS,  
20 DOMO, PRODOM, and hidden Markov model (HMM)-based protein family databases such as PFAM. (HMM is a probabilistic approach which analyzes consensus primary structures of gene families. See, for example, Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.) The queries were performed using programs based on BLAST, FASTA, BLIMPS, and HMMR. The Incyte cDNA sequences were assembled to produce polynucleotide sequences. Alternatively, GenBank cDNAs,  
25 GenBank ESTs, stitched sequences, stretched sequences, or Genscan-predicted coding sequences (see Examples IV and V) were used to extend Incyte cDNA assemblages to full length. Assembly was performed using programs based on Phred, Phrap, and Consed, and cDNA assemblages were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The polynucleotide sequences were translated to derive the corresponding polypeptide sequences which were  
30 subsequently analyzed by querying against databases such as the GenBank protein databases (genpept), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and hidden Markov model (HMM)-based protein family databases such as PFAM. Full length polynucleotide sequences are also analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments are  
35 generated using default parameters specified by the CLUSTAL algorithm as incorporated into the

MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

Table 7 summarizes the tools, programs, and algorithms used for the analysis and assembly of Incyte cDNA and assembled polynucleotide sequences and provides applicable descriptions, references, and threshold parameters. The first column of Table 7 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score or the lower the probability value, the greater the identity between two sequences).

The programs described above for the assembly and analysis of polynucleotide and polypeptide sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:40-78. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies are described in Table 4, column 4.

#### IV. Identification and Editing of Coding Sequences from Genomic DNA

Putative G-protein coupled receptors were initially identified by running the Genscan gene identification program against public genomic sequence databases (e.g., gbpri and gbhtg). Genscan is a general-purpose gene identification program which analyzes genomic DNA sequences from a variety of organisms (See Burge, C. and S. Karlin (1997) *J. Mol. Biol.* 268:78-94, and Burge, C. and S. Karlin (1998) *Curr. Opin. Struct. Biol.* 8:346-354). The program concatenates predicted exons to form an assembled cDNA sequence extending from a methionine to a stop codon. The output of Genscan is a FASTA database of polynucleotide and polypeptide sequences. The maximum range of sequence for Genscan to analyze at once was set to 30 kb. To determine which of these Genscan predicted cDNA sequences encode G-protein coupled receptors, the encoded polypeptides were analyzed by querying against PFAM models for G-protein coupled receptors (7tm\_1, 7tm\_2, 7tm\_3, and 7tm\_4). Potential G-protein coupled receptors were also identified by homology to Incyte cDNA sequences that had been annotated as G-protein coupled receptors. These selected Genscan-predicted sequences were then compared by BLAST analysis to the genpept and gbpri public databases. Where necessary, the Genscan-predicted sequences were then edited by comparison to the top BLAST hit from genpept to correct errors in the sequence predicted by Genscan, such as extra or omitted exons. BLAST analysis was also used to find any Incyte cDNA or public cDNA coverage of the Genscan-predicted sequences, thus providing evidence for transcription. When Incyte cDNA coverage was available, this information was used to correct or confirm the Genscan predicted sequence. Polynucleotide sequences, including SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:61, SEQ ID NO:62,

and SEQ ID NO:63, were obtained by assembling Genscan-predicted coding sequences with Incyte cDNA sequences and/or public cDNA sequences using the assembly process described in Example III. Alternatively, polynucleotide sequences, including SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, and SEQ ID NO:78, are full length coding regions derived entirely from edited or unedited Genscan-predicted coding sequences. Alternatively, polynucleotide sequences, including SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56, are partial genes derived from the assembly and editing of Genscan-predicted sequences only.

#### **V. Assembly of Genomic Sequence Data with cDNA Sequence Data**

##### **"Stitched" Sequences**

Partial cDNA sequences were extended with exons predicted by the Genscan gene identification program described in Example IV. Partial cDNAs assembled as described in Example III were mapped to genomic DNA and parsed into clusters containing related cDNAs and Genscan exon predictions from one or more genomic sequences. Each cluster was analyzed using an algorithm based on graph theory and dynamic programming to integrate cDNA and genomic information, generating possible splice variants that were subsequently confirmed, edited, or extended to create a full length sequence.

Sequence intervals in which the entire length of the interval was present on more than one sequence in the cluster were identified, and intervals thus identified were considered to be equivalent by transitivity. For example, if an interval was present on a cDNA and two genomic sequences, then all three intervals were considered to be equivalent. This process allows unrelated but consecutive genomic sequences to be brought together, bridged by cDNA sequence. Intervals thus identified were then "stitched" together by the stitching algorithm in the order that they appear along their parent sequences to generate the longest possible sequence, as well as sequence variants. Linkages between intervals which proceed along one type of parent sequence (cDNA to cDNA or genomic sequence to genomic sequence) were given preference over linkages which change parent type (cDNA to genomic sequence). The resultant stitched sequences were translated and compared by BLAST analysis to the genpept and gbpr public databases. Incorrect exons predicted by Genscan were corrected by comparison to the top BLAST hit from genpept. Sequences were further extended with additional cDNA sequences, or by inspection of genomic DNA, when necessary.

##### **"Stretched" Sequences**

Partial DNA sequences were extended to full length with an algorithm based on BLAST analysis. First, partial cDNAs assembled as described in Example III were queried against public

databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases using the BLAST program. The nearest GenBank protein homolog was then compared by BLAST analysis to either Incyte cDNA sequences or GenScan exon predicted sequences described in Example IV. A chimeric protein was generated by using the resultant high-scoring segment pairs (HSPs) to map the translated sequences onto the GenBank protein homolog. Insertions or deletions may occur in the chimeric protein with respect to the original GenBank protein homolog. The GenBank protein homolog, the chimeric protein, or both were used as probes to search for homologous genomic sequences from the public human genome databases. Partial DNA sequences were therefore "stretched" or extended by the addition of homologous genomic sequences. The resultant stretched sequences were examined to determine whether it contained a complete gene.

#### VI. Chromosomal Mapping of GCREC Encoding Polynucleotides

The sequences which were used to assemble SEQ ID NO:40-78 were compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:40-78 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 7). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO., to that map location.

Map locations are represented by ranges, or intervals, or human chromosomes. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site (<http://www.ncbi.nlm.nih.gov/genemap/>), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

#### VII. Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, *supra*, ch. 7; Ausubel (1995) *supra*, ch. 4 and 16.)



Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar.

- 5 The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score} \times \text{Percent Identity}}{5 \times \text{minimum} \{ \text{length}(\text{Seq. 1}), \text{length}(\text{Seq. 2}) \}}$$

- 10 The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for  
 15 every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and  
 20 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

- Alternatively, polynucleotide sequences encoding GCREC are analyzed with respect to the tissue sources from which they were derived. For example, some full length sequences are assembled, at least in part, with overlapping Incyte cDNA sequences (see Example III). Each cDNA sequence is  
 25 derived from a cDNA library constructed from a human tissue. Each human tissue is classified into one of the following organ/tissue categories: cardiovascular system; connective tissue; digestive system; embryonic structures; endocrine system; exocrine glands; genitalia, female; genitalia, male; germ cells; hemic and immune system; liver; musculoskeletal system; nervous system; pancreas; respiratory system; sense organs; skin; stomatognathic system; unclassified/mixed; or urinary tract. The number of  
 30 libraries in each category is counted and divided by the total number of libraries across all categories. Similarly, each human tissue is classified into one of the following disease/condition categories: cancer, cell line, developmental, inflammation, neurological, trauma, cardiovascular, pooled, and other, and the number of libraries in each category is counted and divided by the total number of libraries across all categories. The resulting percentages reflect the tissue- and disease-specific expression of cDNA  
 35 encoding GCREC. cDNA sequences and cDNA library/tissue information are found in the LIFESEQ

GOLD database (Incyte Genomics, Palo Alto CA).

#### VIII. Extension of GCREC Encoding Polynucleotides

Full length polynucleotide sequences were also produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One  
5 primer was synthesized to initiate 5' extension of the known fragment, and the other primer was synthesized to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin  
10 structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction  
15 mix contained DNA template, 200 nmol of each primer, reaction buffer containing  $Mg^{2+}$ ,  $(NH_4)_2SO_4$ , and 2-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the  
20 alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100  $\mu$ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE  
25 and 0.5  $\mu$ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5  $\mu$ l to 10  $\mu$ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose gel to determine which reactions were successful in extending the sequence.

30 The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviII cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were

religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems).

In like manner, full length polynucleotide sequences are verified using the above procedure or are used to obtain 5' regulatory sequences using the above procedure along with oligonucleotides designed for such extension, and an appropriate genomic library.

#### **IX. Labeling and Use of Individual Hybridization Probes**

Hybridization probes derived from SEQ ID NO:40-78 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250  $\mu$ Ci of [ $\gamma$ -<sup>32</sup>P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10<sup>7</sup> counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and

compared.

#### X. Microarrays

The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, supra), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Schena (1999), supra). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645; Marshall, A. and J. Hodgson (1998) Nat. Biotechnol. 16:27-31.)

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser desorption and mass spectrometry may be used for detection of hybridization. The degree of complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is described in detail below.

#### 25 Tissue or Cell Sample Preparation

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and poly(A)<sup>+</sup> RNA is purified using the oligo-(dT) cellulose method. Each poly(A)<sup>+</sup> RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/μl oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/μl RNase inhibitor, 500 μM dATP, 500 μM dGTP, 500 μM dTTP, 40 μM dCTP, 40 μM dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)<sup>+</sup> RNA with GEMBRIGHT kits (Incyte). Specific control poly(A)<sup>+</sup> RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA. After incubation at 37° C for 2 hr, each reaction sample (one with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85° C to stop the reaction and degrade the RNA. Samples are purified

using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and

5 resuspended in 14  $\mu$ l 5X SSC/0.2% SDS.

#### **Microarray Preparation**

Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are  
10 amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5  $\mu$ g. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water  
15 washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in US  
20 Patent No. 5,807,522, incorporated herein by reference. 1  $\mu$ l of the array element DNA, at an average concentration of 100 ng/ $\mu$ l, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water.  
25 Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60°C followed by washes in 0.2% SDS and distilled water as before.

#### **Hybridization**

Hybridization reactions contain 9  $\mu$ l of sample mixture consisting of 0.2  $\mu$ g each of Cy3 and  
30 Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65°C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm<sup>2</sup> coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140  $\mu$ l of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for  
35 about 6.5 hours at 60°C. The arrays are washed for 10 min at 45°C in a first wash buffer (1X SSC,

0.1% SDS), three times for 10 minutes each at 45°C in a second wash buffer (0.1X SSC), and dried.

#### Detection

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477, Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital (A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

## XI. Complementary Polynucleotides

Sequences complementary to the GCREC-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring GCREC. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of GCREC. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the GCREC-encoding transcript.

## XII. Expression of GCREC

Expression and purification of GCREC is achieved using bacterial or virus-based expression systems. For expression of GCREC in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express GCREC upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of GCREC in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding GCREC by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, GCREC is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from GCREC at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification

using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, *supra*, ch. 10 and 16). Purified GCREC obtained by these methods can be used directly in the assays shown in Examples XVI, XVII, and XVIII, where applicable.

### XIII. Functional Assays

GCREC function is assessed by expressing the sequences encoding GCREC at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include PCMV SPORT (Life Technologies) and PCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10  $\mu$ g of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2  $\mu$ g of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) *Flow Cytometry*, Oxford, New York NY.

The influence of GCREC on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding GCREC and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding GCREC and other genes of interest can be analyzed by northern analysis or



microarray techniques.

#### **XIV. Production of GCREC Specific Antibodies**

GCREC substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the GCREC amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, *supra*, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Applied Biosystems) using Fmoc chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, *supra*.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-GCREC activity by, for example, binding the peptide or GCREC to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

#### **XV. Purification of Naturally Occurring GCREC Using Specific Antibodies**

Naturally occurring or recombinant GCREC is substantially purified by immunoaffinity chromatography using antibodies specific for GCREC. An immunoaffinity column is constructed by covalently coupling anti-GCREC antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing GCREC are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of GCREC (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/GCREC binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and GCREC is collected.

#### **XVI. Identification of Molecules Which Interact with GCREC**

Molecules which interact with GCREC may include agonists and antagonists, as well as molecules involved in signal transduction, such as G proteins. GCREC, or a fragment thereof, is labeled with <sup>125</sup>I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) *Biochem. J.* 133:529-539.) A fragment of GCREC includes, for example, a fragment comprising one or more of the three extracellular loops, the extracellular N-terminal region, or the third intracellular loop. Candidate

molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled GCREC, washed, and any wells with labeled GCREC complex are assayed. Data obtained using different concentrations of GCREC are used to calculate values for the number, affinity, and association of GCREC with the candidate ligand molecules.

5           Alternatively, molecules interacting with GCREC are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989) *Nature* 340:245-246, or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech). GCREC may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between  
10 the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

Potential GCREC agonists or antagonists may be tested for activation or inhibition of GCREC receptor activity using the assays described in sections XVII and XVIII. Candidate molecules may be selected from known GPCR agonists or antagonists, peptide libraries, or combinatorial chemical  
15 libraries.

Methods for detecting interactions of GCREC with intracellular signal transduction molecules such as G proteins are based on the premise that internal segments or cytoplasmic domains from an orphan G protein-coupled seven transmembrane receptor may be exchanged with the analogous domains of a known G protein-coupled seven transmembrane receptor and used to identify the G-  
20 proteins and downstream signaling pathways activated by the orphan receptor domains (Kobilka, B.K. et al. (1988) *Science* 240:1310-1316). In an analogous fashion, domains of the orphan receptor may be cloned as a portion of a fusion protein and used in binding assays to demonstrate interactions with specific G proteins. Studies have shown that the third intracellular loop of G protein-coupled seven transmembrane receptors is important for G protein interaction and signal transduction  
25 (Conklin, B.R. et al. (1993) *Cell* 73:631-641). For example, the DNA fragment corresponding to the third intracellular loop of GCREC may be amplified by the polymerase chain reaction (PCR) and subcloned into a fusion vector such as nGEX (Pharmacia Biotech). The construct is transformed into

saline. Bound G subunits are detected by [<sup>32</sup>P]ADP-ribosylation with pertussis or cholera toxins. The reactions are terminated by the addition of SDS sample buffer (4.6% (w/v) SDS, 10% (v/v) β-mercaptoethanol, 20% (w/v) glycerol, 95.2 mM Tris-HCl, pH 6.8, 0.01% (w/v) bromphenol blue). The [<sup>32</sup>P]ADP-labeled proteins are separated on 10% SDS-PAGE gels, and autoradiographed. These  
5 gels are transferred to nitrocellulose paper, blocked with blotto (5% nonfat dried milk, 50 mM Tris-HCl (pH 8.0), 2 mM CaCl<sub>2</sub>, 80 mM NaCl, 0.02% NaN<sub>3</sub>, and 0.2% Nonidet P-40) for 1 hour at room temperature, followed by incubation for 1.5 hours with Gα subtype selective antibodies (1:500; Calbiochem-Novabiochem). After three washes, blots are incubated with horseradish peroxidase (HRP)-conjugated goat anti-rabbit immunoglobulin (1:2000, Cappel, Westchester PA) and visualized  
10 by the chemiluminescence-based ECL method (Amersham Corp.).

#### XVII. Demonstration of GCREC Activity

An assay for GCREC activity measures the expression of GCREC on the cell surface. cDNA encoding GCREC is transfected into an appropriate mammalian cell line. Cell surface proteins are labeled with biotin as described (de la Fuente, M.A. et al. (1997) Blood 90:2398-2405).

- 15 Immunoprecipitations are performed using GCREC-specific antibodies, and immunoprecipitated samples are analyzed using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting techniques. The ratio of labeled immunoprecipitant to unlabeled immunoprecipitant is proportional to the amount of GCREC expressed on the cell surface.

- In the alternative, an assay for GCREC activity is based on a prototypical assay for  
20 ligand/receptor-mediated modulation of cell proliferation. This assay measures the rate of DNA synthesis in Swiss mouse 3T3 cells. A plasmid containing polynucleotides encoding GCREC is added to quiescent 3T3 cultured cells using transfection methods well known in the art. The transiently transfected cells are then incubated in the presence of [<sup>3</sup>H]thymidine, a radioactive DNA precursor molecule. Varying amounts of GCREC ligand are then added to the cultured cells. Incorporation of  
25 [<sup>3</sup>H]thymidine into acid-precipitable DNA is measured over an appropriate time interval using a radioisotope counter, and the amount incorporated is directly proportional to the amount of newly synthesized DNA. A linear dose-response curve over at least a hundred-fold GCREC ligand concentration range is indicative of receptor activity. One unit of activity per milliliter is defined as the concentration of GCREC producing a 50% response level, where 100% represents maximal  
30 incorporation of [<sup>3</sup>H]thymidine into acid-precipitable DNA (McKay, I. and I. Leigh, eds. (1993) Growth Factors: A Practical Approach, Oxford University Press, New York NY, p. 73.)

- In a further alternative, the assay for GCREC activity is based upon the ability of GPCR family proteins to modulate G protein-activated second messenger signal transduction pathways (e.g., cAMP; Gaudin, P. et al. (1998) J. Biol. Chem. 273:4990-4996). A plasmid encoding GCREC is  
35 transfected into a mammalian cell line (e.g., Chinese hamster ovary (CHO) or human embryonic

kidney (HEK-293) cell lines) using methods well-known in the art. Transfected cells are grown in 12-well trays in culture medium for 48 hours, then the culture medium is discarded, and the attached cells are gently washed with PBS. The cells are then incubated in culture medium with or without ligand for 30 minutes, then the medium is removed and cells lysed by treatment with 1 M perchloric acid. The cAMP levels in the lysate are measured by radioimmunoassay using methods well-known in the art. Changes in the levels of cAMP in the lysate from cells exposed to ligand compared to those without ligand are proportional to the amount of GCREC present in the transfected cells.

To measure changes in inositol phosphate levels, the cells are grown in 24-well plates containing  $1 \times 10^5$  cells/well and incubated with inositol-free media and [ $^3\text{H}$ ]myoinositol, 2  $\mu\text{Ci}$ /well, for 48 hr. The culture medium is removed, and the cells washed with buffer containing 10 mM LiCl followed by addition of ligand. The reaction is stopped by addition of perchloric acid. Inositol phosphates are extracted and separated on Dowex AG1-X8 (Bio-Rad) anion exchange resin, and the total labeled inositol phosphates counted by liquid scintillation. Changes in the levels of labeled inositol phosphate from cells exposed to ligand compared to those without ligand are proportional to the amount of GCREC present in the transfected cells.

#### XVIII. Identification of GCREC Ligands

GCREC is expressed in a eukaryotic cell line such as CHO (Chinese Hamster Ovary) or HEK (Human Embryonic Kidney) 293 which have a good history of GPCR expression and which contain a wide range of G-proteins allowing for functional coupling of the expressed GCREC to downstream effectors. The transformed cells are assayed for activation of the expressed receptors in the presence of candidate ligands. Activity is measured by changes in intracellular second messengers, such as cyclic AMP or  $\text{Ca}^{2+}$ . These may be measured directly using standard methods well known in the art, or by the use of reporter gene assays in which a luminescent protein (e.g. firefly luciferase or green fluorescent protein) is under the transcriptional control of a promoter responsive to the stimulation of protein kinase C by the activated receptor (Milligan, G. et al. (1996) Trends Pharmacol. Sci. 17:235-237). Assay technologies are available for both of these second messenger systems to allow high throughput readout in multi-well plate format, such as the adenylyl cyclase activation FlashPlate Assay (NEN Life Sciences Products), or fluorescent  $\text{Ca}^{2+}$  indicators such as Fluo-4 AM (Molecular Probes) in combination with the FLIPR fluorimetric plate reading system (Molecular Devices). In cases where the physiologically relevant second messenger pathway is not known, GCREC may be coexpressed with the G-proteins  $\text{G}_{\alpha 15/16}$  which have been demonstrated to couple to a wide range of G-proteins (Offermanns, S. and M.I. Simon (1995) J. Biol. Chem. 270:15175-15180), in order to funnel the signal transduction of the GCREC through a pathway involving phospholipase C and  $\text{Ca}^{2+}$  mobilization. Alternatively, GCREC may be expressed in engineered yeast systems which lack endogenous GPCRs, thus providing the advantage of a null background for GCREC activation screening. These yeast systems substitute a

human GPCR and Ga protein for the corresponding components of the endogenous yeast pheromone receptor pathway. Downstream signaling pathways are also modified so that the normal yeast response to the signal is converted to positive growth on selective media or to reporter gene expression (Broach, J.R. and J. Thorner (1996) Nature 384 (supp.):14-16). The receptors are screened against putative  
5 ligands including known GPCR ligands and other naturally occurring bioactive molecules. Biological extracts from tissues, biological fluids and cell supernatants are also screened.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention.  
10 Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Incyte Project ID	Polypeptide SEQ ID NO:	Incyte Polypeptide ID	Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID
104941	1	104941CD1	40	104941CB1
1499408	2	1499408CD1	41	1499408CB1
3168839	3	3168839CD1	42	3168839CB1
3291235	4	3291235CD1	43	3291235CB1
7472001	5	7472001CD1	44	7472001CB1
7472003	6	7472003CD1	45	7472003CB1
7472004	7	7472004CD1	46	7472004CB1
7475687	8	7475687CD1	47	7475687CB1
7483029	9	7483029CD1	48	7483029CB1
7477933	10	7477933CD1	49	7477933CB1
7475164	11	7475164CD1	50	7475164CB1
7473909	12	7473909CD1	51	7473909CB1
7475252	13	7475252CD1	52	7475252CB1
7927572	14	7927572CD1	53	7927572CB1
7481257	15	7481257CD1	54	7481257CB1
7485790	16	7485790CD1	55	7485790CB1
7482993	17	7482993CD1	56	7482993CB1
2829053	18	2829053CD1	57	2829053CB1
3068234	19	3068234CD1	58	3068234CB1
5029478	20	5029478CD1	59	5029478CB1
5102576	21	5102576CD1	60	5102576CB1
2200534	22	2200534CD1	61	2200534CB1
3275821	23	3275821CD1	62	3275821CB1
3744167	24	3744167CD1	63	3744167CB1
7472007	25	7472007CD1	64	7472007CB1
7472008	26	7472008CD1	65	7472008CB1
7472013	27	7472013CD1	66	7472013CB1
7472015	28	7472015CD1	67	7472015CB1
7472016	29	7472016CD1	68	7472016CB1

Table 1 (cont.)

Incyte Project ID	Polypeptide SEQ ID NO:	Incyte Polypeptide ID	Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID
7472017	30	7472017CD1	69	7472017CBI
7472018	31	7472018CD1	70	7472018CBI
7472019	32	7472019CD1	71	7472019CBI
7472021	33	7472021CD1	72	7472021CBI
7472009	34	7472009CD1	73	7472009CBI
7472010	35	7472010CD1	74	7472010CBI
7472011	36	7472011CD1	75	7472011CBI
7472012	37	7472012CD1	76	7472012CBI
7472014	38	7472014CD1	77	7472014CBI
7472020	39	7472020CD1	78	7472020CBI

Table 2

Polypeptide SEQ ID NO:	Incyte polypeptide ID	GenBank ID NO:	Probability Score	GenBank Homolog
1	104941CD1	g7211316	6.9E-146	Olfactory receptor [Callithrix jacchus]
2	1499408CD1	g202806	5.20E-162	Vasopressin receptor [Rattus norvegicus]
3	3168839CD1	g3618229	2.2E-44	G protein-linked P2Y4 receptor [Rattus norvegicus]
4	3291235CD1	g3287369	1.40E-126	A-2 [Mus musculus]
5	7472001CD1	g1256393	2.20E-122	Taste bud receptor protein TB 641 [Rattus norvegicus]
6	7472003CD1	g4378765	1.20E-169	Orphan G protein-coupled receptor GPR54 [Rattus norvegicus]
7	7472004CD1	g1698952	6.30E-118	High-affinity lysophosphatidic acid receptor [Xenopus laevis]
8	7475687CP1	g1256393	4.70E-90	Taste bud receptor protein TB 641 [Rattus norvegicus]
9	7483029CP1	g2447219	2.50E-75	OLF4 [Homo sapiens]
10	7477933CP1	g2792016	4.90E-79	Olfactory receptor [Homo sapiens]
11	7475164CP1	g517366	3.00E-111	Olfactory receptor [Rattus norvegicus]
12	7473909CP1	g4680264	1.90E-22	Odorant receptor S25 [Mus musculus]
13	7475252CP1	g2447219	6.50E-61	OLF4 [Homo sapiens]
14	7927572CP1	g8100089	6.7E-54	Putative taste receptor HTR2 [Homo sapiens]
15	7481257CP1	g4826521	4.00E-29	dJ88J8.1 (novel 7 transmembrane receptor (rhodopsin family) (olfactory receptor like protein (hs6M1-15)) [Homo sapiens])
16	7485790CP1	g2447219	3.00E-40	OLF4 [Homo sapiens]
17	7482993CP1	g1314665	3.10E-54	CfOLF3 [Canis familiaris]
18	2829053CD1			
19	3068234CD1	g5922725	3.1E-190	Lysophosphatidic acid G protein-coupled receptor [Homo sapiens]
20	5029478CD1	g1049072	3.6E-21	Galanin receptor GALR1 [Rattus norvegicus] (Cloning and characterization of the rat GALR1 galanin receptor from RIN14B insulinoma cells. Brain Res. Mol. Brain Res. 1995 Dec 28;34(2):179-189.)



Table 2 (cont.)

Polypeptide SEQ ID NO:	Incyte Polypeptide ID	GenBank ID NO:	Probability Score	GenBank Homolog
21	5102576CD1	g2792016	2.4E-92	Olfactory receptor [Homo sapiens] (Molecular cloning and chromosomal mapping of olfactory receptor genes expressed in the male germ line: evidence for their wide distribution in the human genome. Biochem. Biophys. Res. Commun. 1997 Aug 18;237(2):283-287.)
22	2200534CD1	g5051404	4.6e-131	573K1.15 (mm17M1-6) 7-transmembrane olfactory receptor-like protein (rhodopsin family) [Mus musculus]
23	3275821CD1	g182742	1.5e-29	Formyl peptide receptor [Homo sapiens] (Murphy, P.M. et al. (1992) J. Biol. Chem. 267:7637-7643)
24	3744167CD1	g9186902	1.2E-240	Leukotriene B4 receptor, BLT2 [Mus musculus]
25	7472007CD1	g7638409	1.3E-199	Olfactory receptor P2 [Mus musculus]
26	7472008CD1	g4218182	1.0e-89	cd271M21.2 (hs6M1-12 (7 transmembrane receptor (rhodopsin family) (olfactory receptor like) protein)) [Homo sapiens]
27	7472013CD1	g205846	2.5e-70	Olfactory protein [Rattus norvegicus]
28	7472015CD1	g1204095	2.5e-25	Dopamine receptor [Fugu rubripes]
29	7472016CD1	g6090796	1.1E-215	Olfactory receptor [Gorilla gorilla]
30	7472017CD1	g3757727	2.0e-61	cd80I19.7 (olfactory receptor-like protein (hs6M1-3)) [Homo sapiens]
31	7472018CD1	g5644328	2.3E-112	Orphan G protein-coupled receptor GPR26 [Rattus norvegicus]
32	7472019CD1	g5869916	2.7e-73	Olfactory receptor [Mus musculus]
33	7472021CD1	g6090804	2.6E-94	Olfactory receptor [Gorilla gorilla]
34	7472009CD1	g1016362	1.6e-68	OLI receptor [Rattus norvegicus]
35	7472010CD1	g2317704	7.3e-80	Olfactory receptor [Rattus norvegicus]
36	7472011CD1	g6178008	4.9E-114	Odorant receptor MOR18 [Mus musculus]
37	7472012CD1	g205816	6.8e-84	Olfactory protein [Rattus norvegicus]
38	7472014CD1	g205816	3.9e-88	Olfactory protein [Rattus norvegicus]
39	7472020CD1	g2792016	1.9e-97	Olfactory receptor [Homo sapiens]

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
1	104941CD1	311	S68 S189 S292 Y310	N5 N66	7 transmembrane receptor (rhodopsin family): G42-Y291 GPCR signature: K91-P130, I208-Y219, Y283-K399, Y103-S151 Olfactory receptor signature: M60-K81, F178-D192, F239-G254, A275-L286, S292-Q306 Transmembrane domains: I31-I47, P211-I229	MOTIFS HMMER-PFAM BLIMPS- BLOCKS BLIMPS- PRINTS ProfileScan
2	1499408CD1	891	T148 S686 S114 S248 S350 S481 S501 T628 T814 S856 T84 S140 T144 T325 T411 T543 S568 S676 T706 T788 Y372	N378	ATP/GTP binding site (P-loop): G202-T209	MOTIFS
3	3168839CD1	422	T232 S178 T342 S363 S371 S397 T21 S211 S226 T307 S332 S367	N4 N9 N251 N323	7 transmembrane receptor (rhodopsin family): L39-Y297 Rhodopsin-like GPCR superfamily: L24-L48, V57-R78, F101-I123, V137-R158, V192-F215, T232-V256, L279-R305 Transmembrane domains: V275-L295	MOTIFS HMMER-PFAM BLIMPS- BLOCKS ProfileScan BLIMPS- PRINTS HMMER
4	3291235CD1	609	S228 S229 S396 S456 S324 S328 S364 S417 S466 T506 S568 S590 S153 S268 T392 S462 S482 S560 Y348		7 transmembrane receptor (rhodopsin family): E80-E154 GPCR signatures: F76-P115, F395-A405,, A442-E458, E509-P526 Transmembrane domain: V174-L199	MOTIFS HMMER-PFAM BLIMPS- BLOCKS BLIMPS- PRINTS HMMER

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
5	7472001CD1	313	S68 T194 T200 S267 T309 T138 T164 T290 S306	N5 N85	7 transmembrane receptor (rhodopsin family): G41-I259 GPCR signature: K91-P130, T281-K297, Y103-A147 Olfactory receptor signature: M60-R81, F178-D192, F239-V254, A273-L284, T290-L304 Signal peptide: M1-T38	MOTIFS HMNER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfileScan
					Transmembrane domains: F30-T48, F63-M83	HMNER SPScan
6	7472003CD1	398	S36 T155	N10 N18 N28	7 transmembrane receptor (rhodopsin family): G59-Y323 GPCR signature: W108-P147, Y213-Y224, A256-F282, N315-R331, N119-I166 Neuropeptide Y receptor signature: R69-I81, L321-F334	MOTIFS HMNER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfileScan
					Transmembrane domain: A42-Y65	HMNER
7	7472004CD1	369	S228 T94 T218 S339 T350	N12	7 transmembrane receptor (rhodopsin family): G48-Y321 Rhodopsin-like GPCR signature: T33-Y57, I66-F87, F111-I133, R144-V165, V193-L216, A262-V286, S303-H329 Transmembrane domains: T33-V51, M109-I125, Y189-M213, M256-V275	MOTIFS HMNER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
					Transmembrane domains: T33-V51, M109-I125, Y189-M213, M256-V275	HMNER
8	7475687CPI	194	T186 T76 T82 T46 T172		7 transmembrane receptor (rhodopsin family): M1-Y171 Opsins retinal binding site: Y142-N194 Olfactory receptor signature: F60-D74, F121-V136, A155-L166, T172-T186	MOTIFS HMNER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfileScan

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
9	7483029CP1	173	T16 S34 T60	N32 N167	7 transmembrane receptor (rhodopsin family): G8-C146 Rhodopsin-like GPCR signature: M26-K47, F71-I93, L107-I128	MOTIFS HMMER-PFAM BLIMPS- BLOCKS ProfileScan BLIMPS- PRINTS SPScan HMMER
10	7477933CP1	220	S172		Signal peptide: M1-L22  Transmembrane domains: M68-A86, M103-L121 7 transmembrane receptor (rhodopsin family): P1-C192 Olfactory receptor signature: M2-K23, F120-D134, F181-G196 Rhodopsin-like GPCR signature: L47-I69, I142-V165 Transmembrane domains: M44-A62, V85-T110	MOTIFS HMMER-PFAM BLIMPS- BLOCKS BLIMPS- PRINTS  HMMER
11	7475164CP1	302	T296 S58 S84 T107 T257 T9 T69 S128 T151 S282		7 transmembrane receptor (rhodopsin family): G32-I193 GPCR signature: N81-P120, I273-K289, S93-L142 Olfactory receptor signature: V50-K71, Y168-S182, F229-G244, S265-L276, S282-T296 Transmembrane domains: F19-L39, I188-I207	MOTIFS HMMER-PFAM BLIMPS- BLOCKS ProfileScan BLIMPS- PRINTS  HMMER
12	7473909CP1	110	S70 S36 T66 S94		GPCR signature: I85-K101 Olfactory receptor signature: F41-G56, A77-L88, S94-Y108	MOTIFS BLIMPS- BLOCKS BLIMPS- PRINTS

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
13	7475252CP1	178	S66 S151 S136	N4 N64	7 transmembrane receptor (rhodopsin family): G40-L153 Rhodopsin-like GPCR signature: V25-S49, M58-K79, L103-I125, S102-S151  Transmembrane domains: L29-I45, M100-M117 Olfactory receptor signature: F25-D39	MOTIFS HMME-PFAM BLIMPS- BLOCKS ProfileScan BLIMPS- PRINTS HMME
14	7927572CP1	92				MOTIFS BLIMPS- PRINTS
15	7481257CP1	97			7 transmembrane receptor (rhodopsin family): M1-Y96 GPCR signature: V13-Y24, Q41-Q67 Olfactory receptor signature: F44-G59, L80-L91 Signal peptide: M1-G27	MOTIFS HMME-PFAM BLIMPS- BLOCKS BLIMPS- PRINTS SPScan HMME
16	7485790CP1	133	S74		Transmembrane domain: M8-Y24 7 transmembrane receptor (rhodopsin family): R22-V128 GPCR signature: G71-P110	MOTIFS HMME-PFAM BLIMPS- BLOCKS BLIMPS- PRINTS HMME
17	7482993CP1	213	S85 S205 S159 T183	N83	Transmembrane domain: M82-A100 7 transmembrane receptor (rhodopsin family): S2-Y182 GPCR signature: R127-R153, S2-A38 Olfactory receptor signature: F69-N83, F130-G145, V166-L177, T183-G197 Transmembrane domains: P102-I120, F130-V152	MOTIFS HMME-PFAM BLIMPS- BLOCKS ProfileScan BLIMPS- PRINTS HMME

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
18	2829053CD1	180	S30 S41 S109 S125 S140 S35 S36 S149		Beta-1 adrenergic receptor signature: I148-S166 Signal peptide: M1-S67	MOTIFS BLIMPS- PRINTS SPScan
19	3068234CD1	353	T146 T217 T233 S321 S17 T21 S294 S329 T141 S229 T303 Y14	N15 N139 N172 N349	7 transmembrane receptor (rhodopsin family): S47-Y293 Rhodopsin-like GPCR superfamily signature: I32-I56, F65-L86, L109-I131, R144-L165, Y187-Y210, L237-L261, K275-Y301 Transmembrane domains: V36-I56, T146-G166, Y187-L207, T240-V258	MOTIFS HMMER-PFAM BLIMPS- BLOCKS BLIMPS- PRINTS HMMER
20	5029478CD1	361	T242 S256 S237 S350	N21 N322	7 transmembrane receptor (rhodopsin family): G57-Y321 Rhodopsin-like GPCR superfamily signature: V42-A66, T74-V95, M118-I140, A154-V175, D208-L231, L262-L286, F303-E329 Transmembrane domains: T45-V65, V124-Q144, V209-I233, L266-N291	MOTIFS HMMER-PFAM BLIMPS- BLOCKS BLIMPS- PRINTS HMMER
21	5102576CD1	251	S119 S196		7 transmembrane receptor (rhodopsin family): R8-C251 GPCR signature: R57-P96 Olfactory receptor signature: M26-K47, L144-D158, F205-G220, A241-C252 Transmembrane domains: T66-D88, V109-T134	MOTIFS HMMER-PFAM BLIMPS- BLOCKS BLIMPS- PRINTS HMMER

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
22	2200534CD1	315	S6 S136 T291	N4 N154	G-protein coupled receptor: DM00013(P232750)17-306: S17-L305 DM00013(A570690)15-304: F16-L305 DM00013(P47881)20-309: P20-L305 PD149621: T246-L305 PD000921: C168-L245 PD002495: N4-L47 BL00237: L89-P128, L207-Y218, T282-K298 Olfactory receptor PR00245: M58-P79, F176-G190, V238-G253, V274-L285, T291-L305 G-protein coupled receptors	HMNER BLIMPS- PRINTS BLIMPS- BLOCKS HMNER-PFAM MOTIFS
23	3275821CD1	470	T3 T18 T326 T332 T340 S350 S424 S451 T459 S192	N47	Transmembrane domains: V204-M228, G40-Y290 G-protein coupled receptor: DM00013(P21462)20-317: V34-L306 PD000009: L68-F169 BL00237: W97-P136, G201-H212, A230-A256, N287-R303 GPCR profile: F109-V155 Rhodopsin GPCR family PR00237: W31-G55, L66-Q87, W111-A133, L147-V168, L193-Q216, F235-L259, L277-R303 G-protein coupled receptors	BLAST- PRODOM BLAST-DOMO HMNER HMNER-PFAM BLIMPS- BLOCKS BLIMPS- PRINTS ProfileScan MOTIFS BLAST- PRODOM BLAST-DOMO HMNER
					Transmembrane domains: T33-A51, L68-L259	

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
24	3744167CD1	358	T291 S15 T18 S215	N10 N38 N342	<p>G-protein coupled receptor:  DM00013(P46092)27-318: S19-F290  DM00013(P31391)41-326: L29-L304  DM00013(P35414)22-324: W16-F290  BL00237: W87-F126, F190-Y201,  R217-V243, S280-L296</p> <p>GPCR profile:  Y99-V145</p> <p>Rhodopsin GPCR family PR00237:  T22-A46, A57-F78, C101-V123,  L137-V158, L182-L205, V222-L246,  R270-L296</p> <p>G-protein coupled receptors</p>	<p>HMER-PFAM  BLIMPS-BLOCKS  BLIMPS-PRINTS  ProfilesScan  MOTIFS</p>
					Transmembrane domains: A138-Y159, G37-Y288	<p>BLAST-  PRODOM  BLAST-DOMO  HMER</p>



Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
25	7472007CD1	314	S270 S291 S311 T49 S67 S193	N4 N65	Signal peptide: M1-Q56 Transmembrane domains: L29-V48, L208-M228 7 transmembrane receptor (rhodopsin family) signature: G41-Y290 G-protein coupled receptor signatures: T90-P129, I207-Y218, T282-K298 G-protein coupled receptor signature: Y102-A147 G-protein coupled receptor signature: A110-A125 Olfactory receptor signatures: M59-K80, F177-D191, F238-S253, I274-L285, S291-I305 Melanocortin receptor family: A5-L63 Rhodopsin-like GPCR superfamily: L26-I50, M59-K80, F104-I126, F153-V174, A199-L222, A237-R261, K272-K298 G-protein coupled receptor: DM00013   P23270   18-311: L23-H306 G-protein coupled receptor DM00013   P23267   20-309: L27-I305 G-protein coupled receptor DM00013   P23275   17-306: L23-I305 G-protein coupled receptor DM00013   P30953   18-306: L19-H306 Olfactory receptor PD000921: F168-L246 Olfactory receptor PD149621: V247-R307	SPScan HMWER HMWER-PFAM BLIMPS-BLOCKS ProfileScan MOTIFS BLIMPS-PRINTS BLIMPS-PRINTS BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST- PRODOM BLAST- PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
26	7472008CD1	365	S78 T192 S199 T320 S343 S47 S66 S78 S96 S217 T222 T337 T361	N94	Transmembrane domain: I226-L244 7 transmembrane receptor (rhodopsin family) signature: G70-Y319 G-protein coupled receptor signatures: K119-P158, L236-S247, K264-Q290, T311-H327 Olfactory receptor signatures: M88-Q109, V206-D220, F267-G282, L303-L314, T320-K334 Melanocortin receptor family: V73-L84, K80-L92 Rhodopsin-like GPCR superfamily: L55-L79, M88-Q109, F133-V155, M228-A251, A266-Q290, K301-H327 Olfactory receptor PD000921: L195-L275 Olfactory receptor PD149621: V276-K331 G-protein coupled receptor: DM00013 P30955 18-305: L61-L326 G-protein coupled receptor: DM00013 P23269 15-304: L61-L326 G-protein coupled receptor DM00013 A57069 15-304: D59-L326 G-protein coupled receptor DM00013 P23275 17-306: T67-L326	HMME HMME-PFAM  BLIMPS-BLOCKS  BLIMPS-PRINTS  BLIMPS-PRINTS  BLAST-PRODOM BLAST-PRODOM BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
27	7472013CD1	317	S68 S193	N6 N22 N43	Signal peptide: M1-G42 Transmembrane domain: I23-L41 7 transmembrane receptor (rhodopsin family) signatures: G42-L155, A279-Y295 G-protein coupled receptor signatures: P91-P130, M212-Y223, T287-K303 G-protein coupled receptor signature: F103-L148 G-protein coupled receptor signature: T111-A126 Olfactory receptor signatures: M60-Q81, F182-D196, V243-G258, A279-A290, S296-L310 Melanocortin receptor family: W52-L64 Rhodopsin-like GPCR superfamily: L27-S51, M60-Q81, F105-I127, R141-G162, I204-G227, A242-Q266, M277-K303 GPR3 orphan receptor signature: V161-N178 G-protein coupled receptor: DM00013 P23274 18-306: L27-L310 G-protein coupled receptor: DM00013 P23272 18-306: Y25-L310 G-protein coupled receptor: DM00013 P30953 18-306: L27-L310 G-protein coupled receptor: DM00013 P30955 18-305: L27-L310 Olfactory receptor PD000921: G174-L250 Olfactory receptor PD149621: T251-L310	SPScan HMMER HMMER-PFAM BLIMPS-BLOCKS ProfileScan MOTIFS BLIMPS-PRINTS BLIMPS-PRINTS BLIMPS-PRINTS BLIMPS-PRINTS BLIMPS-PRINTS BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-PRODROM BLAST-PRODROM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
28	7472015CD1	335	T73 S79 S214 S309 T217 S329 S331		Signal peptide: M1-A20 Signal peptide: M1-A20 Transmembrane domains: F5-V27, L45-T63, M117-I136 7 transmembrane receptor (rhodopsin family) signatures: T21-Y279 G-protein coupled receptor signatures: R71-P110, P174-Y185, P218-T244, N271-R287 G-protein coupled receptor signature: F84-L129 G-protein coupled receptor signature: A91-I106 Rhodopsin-like GPCR superfamily: S6-L30, S40-L61, V85-I107, V121-G142, V166-L189, A223-V247, E261-R287 G-protein coupled receptor: DM00013 P41596 J37-461: G8-D220 G-protein coupled receptor: DM00013 P47800 29-338: G8-Y281 G-protein coupled receptor: DM00013 P31388 20-336: G8-P218 G-protein coupled receptor: DM00013 JN0591 20-336: G8-P218	HMMER SPScan HMMER HMMER-PFAM BLIMPS-BLOCKS ProfileScan MOTIFS BLIMPS-PRINTS BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
29	7472016CD1	309	S8 S67 S188 S266 S137 S229 S266 S289	N5 N65 N264	Signal peptide: M1-L55 Transmembrane domains: Y28-A48, M199-I218 7 transmembrane receptor (rhodopsin family) signatures: G41-Y288 G-protein coupled receptor signatures: K90-P129, F206-Y217, L234-R260, T280-K296 G-protein coupled receptor signature: Y102-A146 Olfactory receptor signatures: M59-K80, F177-D191, F237-G252, I272-L283, S289-F303 Rhodopsin-like GPCR superfamily: F26-C50, M59-K80, M104-I126 S140-L161, M198-F219, A270-K296 G-protein coupled receptor: DM00013 P23266 17-306: Q20-L302 G-protein coupled receptor: DM00013 P23274 18-306: E22-L299 G-protein coupled receptor: DM00013 P23269 15-304: Q21-L299 G-protein coupled receptor: DM00013 P30955 18-305: E22-L302 Olfactory receptor PD149621: T245-S309 Olfactory receptor PD000921: L166-L244	SPScan HMME HMME-PFAM BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-PRODOM BLAST-PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
30	7472017CD1	236	S7 T217	N5 N189	Signal peptide: M1-G42 Transmembrane domains: C31-M52, V123-L141 7 transmembrane receptor (rhodopsin family) signatures: F12-Y216 G-protein coupled receptor signatures: K24-P63, L133-Y144, C161-Q187, T208-K224 G-protein coupled receptor signature: Y36-V81 G-protein coupled receptor signature: T44-A59 G-protein coupled receptor signature: T44-A59 Olfactory receptor signatures: L164-G179, I200-L211, T217-N231 Rhodopsin-like GPCR superfamily: S38-V60, L125-A148, G163-Q187, K198-K224 Olfactory receptor PD149621: V173-T236 Olfactory receptor PD000921: C103-I172 G-protein coupled receptor: DM00013 P23269 15-304: L15-L227 G-protein coupled receptor: DM00013 P30953 18-306: L15-L227 G-protein coupled receptor: DM00013 A57069 15-304: L15-R228 G-protein coupled receptor: DM00013 P23275 17-306: M1-L227	SPScan HMME HMME-PFAM BLIMPS-BLOCKS ProfileScan MOTIFS BLIMPS-PRINTS BLIMPS-PRINTS BLAST-PRODOM BLAST-PRODOM BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
31	7472018CD1	363	Y294 S321 S325 T353 S157 T210 S223 T240 T316 T340	N47 N348 N355	Signal peptide: M1-A24 Signal peptide: M1-A24 7 transmembrane receptor (rhodopsin family) signatures: S22-Y294 G-protein coupled receptor signatures: T72-P111, F181-S192, R234-T260, K286-R302 Rhodopsin-like GPCR superfamily: L7-A31, S41-F62, D86-V108, Y122-G143, T173-H196, A239-A263, G276-R302 P2Y4 purinoceptor signatures: Y32-L48, P111-L126 G-protein coupled receptor: DM00013 JN0591 20-336: P3-L305 G-protein coupled receptor: DM00013 P53452 17-344: L7-F268 G-protein coupled receptor: DM00013 P50406 20-335: G4-L305 G-protein coupled receptor: DM00013 P31388 20-336: P3-L305	HMME SPScan HMME-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
32	7472019CD1	308	S162 S290 S67 T187 S192 S265	N5 N65	Transmembrane domains: L30-I49, M197-L215 7 transmembrane receptor (rhodopsin family) signatures: G41-Y289 G-protein coupled receptor signatures: P90-P129, L206-Y217, L234-K260, T281-K297 G-protein coupled receptor signature: S102-T147 Olfactory receptor signatures: I59-Q80, F176-D190, F237-G252, I273-L284, S290-M304 Melanocortin receptor family: F51-L63 Rhodopsin-like GPCR superfamily: T26-H50, I59-Q80, S104-I126, V140-L161, I198-A221, K271-K297 G-protein coupled receptor: DM00013 P23275 17-306: I17-M304 G-protein coupled receptor: DM00013 P23269 15-304: F27-M304 G-protein coupled receptor: DM00013 P23266 17-306: I17-M304 G-protein coupled receptor: DM00013 S29707 18-306: P21-I300 Olfactory receptor PD000921: L165-L244 Olfactory receptor PD149621: T245-M304	HMME HMME-PFAM BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS BLIMPS-PRINTS BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-PRODROM BLAST-PRODROM



Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
33	7472021CD1	343	S87 T154 S288 S326 S311 S316	N25 N183 N314	Transmembrane domains: Y55-L75, I214-I234 7 transmembrane receptor (rhodopsin family) signatures: G61-Y310 G-protein coupled receptor signatures: S38-L64, G110-P149, P302-K318 G-protein coupled receptor signature: F122-V168 G-protein coupled receptor signature: S130-A145 Olfactory receptor signatures: M79-Q100, F197-Y211, F258-S273, F297-L305, S311-L325 Melanocortin receptor family: V71-L83 Vasopressin receptor signature: L75-L86 Olfactory receptor PD000921: I186-L265 Olfactory receptor PD149621: V267-E328 G-protein coupled receptor: DM00013 P23269 I5-304: E40-L325 G-protein coupled receptor: DM00013 P23275 I7-306: S38-L325 G-protein coupled receptor: DM00013 P23273 I8-306: I45-L325 G-protein coupled receptor: DM00013 P23266 I7-306: S38-S326	HMER HMER-PFAM BLIMPS-BLOCKS ProfileScan MOTIFS BLIMPS-PRINTS BLIMPS-PRINTS BLAST-PRODOM BLAST-PRODOM BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
34	7472009CD1	323	S87 S232 T290 S8 S67 T193	N5	Transmembrane domains: L30-L47, I201-L221 7 transmembrane receptor (rhodopsin family) signatures: G41-Y289 G-protein coupled receptor signatures: K90-P129, L206-Y217, R234-R260, T281-A297 G-protein coupled receptor signature: F102-M147 G-protein coupled receptor signature: A110-A125 Olfactory receptor signatures: M59-K80, F177-D191, P237-G252, G273-L284, T290-L304 Rhodopsin-like GPCR superfamily: F26-C50, Y104-I126, V140-A161, T198-L221, K271-A297 Melanocortin receptor family: I51-L63, I126-N137 Vasopressin receptor signature: L55-L66 G-protein coupled receptor: DM00013   P23275   17-306: L25-L304 G-protein coupled receptor: DM00013   A57069   15-304: L27-L304 G-protein coupled receptor: DM00013   P23270   18-311: L25-L304 G-protein coupled receptor: DM00013   P23266   17-306: L27-L304 Olfactory receptor PD149621: T245-T310 Olfactory receptor PD000921: F168-L244	HMMER HMMER-PFAM BLIMPS-BLOCKS ProfileScan MOTIFS BLIMPS-PRINTS BLIMPS-PRINTS BLIMPS-PRINTS BLIMPS-PRINTS BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-PRODOM BLAST-PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
35	7472010CD1	299	T68 S126 S280 T293 S10 S57 T156	N55	Transmembrane domain: L186-I205 7 transmembrane receptor (rhodopsin family) signatures: G31-Y279 G-protein coupled receptor signatures: S79-P118, F188-S199, S224-T250, V271-K287 G-protein coupled receptor signature: F91-F135 G-protein coupled receptor signature: S99-A114 Olfactory receptor signatures: M49-K70, Y166-S180, F227-G242, A263-L274, S280-L294 Melanocortin receptor family: I41-L53 Rhodopsin-like GPCR superfamily: Q16-G40, M49-K70, F93-I115, T181-V204, A226-T250, R261-K287 G-protein coupled receptor: DM00013   S29709   I1-299: G23-L294 G-protein coupled receptor: DM00013   S51356   I8-307: I24-K292 G-protein coupled receptor: DM00013   P23274   I8-306: I24-L294 G-protein coupled receptor: DM00013   P30955   I8-305: I24-L294 Olfactory receptor PD149621: V237-R296 Olfactory receptor PD000921: L155-I235	HMNER HMNER-PFAM BLIMPS-BLOCKS ProfileScan MOTIFS BLIMPS-PRINTS BLIMPS-PRINTS BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-PRODOM BLAST-PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
36	7472011CD1	307	S87 T288 S193	N5	Transmembrane domains: L23-I43, M98-M118, G204-H228 7 transmembrane receptor (rhodopsin family) signatures: G41-Y287 G-protein coupled receptor signatures: K90-P129, R234-R260, T279-Q295 G-protein coupled receptor signature: F102-T148 Olfactory receptor signatures: M59-K80, F177-D191, A237-V252, V271-L282, T288-G302 Melanocortin receptor family: S51-L63 Rhodopsin-like GPCR superfamily: F26-T50, M59-K80, F104-I126, L140-A161, K199-L222, A236-R260, K269-Q295 Olfactory receptor PD000921: L166-I245 Olfactory receptor PD149621: V246-R303 G-protein coupled receptor: DM00013 S29710 15-301: L17-L301 G-protein coupled receptor: DM00013 P23275 17-306: L17-L301 G-protein coupled receptor: DM00013 P23266 17-306: L17-L301 G-protein coupled receptor: DM00013 P47881 20-309: L23-L301	HMME HMME-PFAM BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS BLIMPS-PRINTS BLIMPS-PRINTS BLAST-PRODOM BLAST-PRODOM BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
37	7472012CD1	314	T19 S230 S291	N5 N38	7 transmembrane receptor (rhodopsin family) signatures: G41-Y290 G-protein coupled receptor signatures: K90-P129, T282-K298 G-protein coupled receptor signature: Y102-M147 G-protein coupled receptor signature: M110-A125 Olfactory receptor signatures: M59-K80, F177-S191, F238-G253, I274-L285, S291-M305 Rhodopsin-like GPCR superfamily: P26-L50, M59-K80, F104-I126, I199-I222, T237-R261, R272-K298 G-protein coupled receptor: DM00013 P23266 17-306: I17-K303 G-protein coupled receptor: DM00013 P23274 18-306: E22-K303 G-protein coupled receptor: DM00013 S29707 18-306: P21-G299 G-protein coupled receptor: DM00013 P30955 18-305: P21-K303 Olfactory receptor PD149621: T246-T310 Olfactory receptor PD000921: L166-L245	HMER-PFAM BLIMPS-BLOCKS ProfileScan MOTIFS BLIMPS-PRINTS BLIMPS-PRINTS BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-PRODOR BLAST-PRODOR

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
38	7472014CD1	310	S19 S67 S93 T267 S18 S137 S290	N5 N265	Transmembrane domains: V30-I46, M59-I78 7 transmembrane receptor (rhodopsin family) signatures: G41-Y289 G-protein coupled receptor signatures: K90-P129, I207-Y218, R235-Q261, T281-K297 G-protein coupled receptor signature: Y102-I151 G-protein coupled receptor signature: T110-A125 Olfactory receptor signatures: M59-K80, F177-S191, P238-G253, A273-L284, S290-M304 Melanocortin receptor family: S51-L63 Rhodopsin-like GPCR superfamily: P26-R50, M59-K80, F104-I126, V199-L222, Q271-K297 Olfactory receptor PD000921: L166-L245 Olfactory receptor PD149621: T246-R306 G-protein coupled receptor: DM00013 P23266 17-306: L17-M304 G-protein coupled receptor: DM00013 P23274 18-306: E22-M304 G-protein coupled receptor: DM00013 P30955 18-305: D23-M304 G-protein coupled receptor: DM00013 P30953 18-306: R20-H305	HMMER HMMER-PFAM BLIMPS-BLOCKS ProfileScan MOTIFS BLIMPS-PRINTS BLIMPS-PRINTS BLAST-PRODOM BLAST-PRODOM BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
39	7472020CD1	359	S257 S317 S178 S255	N31	Transmembrane domains: M127-A145, V168-T193 7 transmembrane receptor (rhodopsin family) signatures: R67-Y316 G-protein coupled receptor signatures: R116-P155, G233-Y244, S261-T287, T308-Q324 G-protein coupled receptor signature: F129-V173 Olfactory receptor signatures: M85-K106, F203-D217, F264-G279, A300-L311, S317-R331 GPR orphan receptor signature: S317-W328 Cannabinoid receptor signatures: M60-L73, Y316-A326 G-protein coupled receptor: DM00013 P23265 I7-306: E45-L327 G-protein coupled receptor: DM00013 P23268 I8-307: S44-L330 G-protein coupled receptor: DM00013 S29707 I8-306: P47-L327 G-protein coupled receptor: DM00013 P30953 I8-306: P47-L330 Olfactory receptor PD000921: N197-L271 Olfactory receptor PD149621: V273-R333	HMNER HMNER-PFAM BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS BLIMPS-PRINTS BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-DOMO BLAST-PRODOM BLAST-PRODOM

Table 4

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
40	104941CB1	936		g4190944.v113.gs_10.edit 104941H1 (BARNOT02)	1 208	936 429
41	1499408CB1	3365		g2335202.v113.gs_4.edit 1499408H1 (SINTBST01) 927003X11 (BRAINT04) 1632960F6 (COLNNT019) 4051362F6 (SINTNOT18) 1426416F6 (SINTBST01) 2925035F6 (SINTNOT04) 927003T6 (BRAINT04)	1 1068 1092 1613 1994 2223 2535 2710	2105 1325 1764 2099 2618 2686 3043 3365
42	3168839CB1	1325		3356166H1 (PROSTUT16) g4589937.v113.gs_7.edit 3700658H1 (SINTNOT05) 3168839H1 (BRSTNOT18) 4555080H1 (KERAUNT01)	1 42 160 809 1084	281 1188 463 1059 1325
43	3291235CB1	2124		3291235X308F1 (BONRFET01) g5578925.v113.gs_2.edit 4720927F6 (BRAHCT02) 3291235F6 (BONRFET01) 3370971H1 (CONNTUT05) 1729983H1 (BRSTTUT08)	1 295 315 408 955 1073	413 2124 810 1004 1208 1293
44	7472001CB1	942		g2121229.v113.gs_4.2.edit	1	942
45	7472003CB1	1197		g3386590.v113.gs_1.edit	1	1197
46	7472004CB1	1110		g4741473.v113.gs_5.edit	1	1110
47	7475687CT1	582		g2121229.v113.gs4.1.nt.edit	1	582
48	7483029CT1	519		g2447218.v113.gs2.nt.edit	1	519
49	747933CT1	663		g2673897.v113.gs7.nt.edit	1	663
50	7475164CT1	911		g3738097.v113.gs2.nt.edit	1	911
51	7473909CT1	332		g3962498.v113.gs3.nt.edit	1	332
52	7475252CT1	538		g4092817.v113.gs1.nt.edit	1	538
53	7927572CT1	279		g5102597.v113.gs2.nt.edit	1	279
54	7481257CT1	291		g5262456.v113.gs4.nt.edit	1	291
55	7485790CT1	402		g5306302.v113.gs6.nt.edit	1	402
56	7482993CT1	639		g5708153.v113.gs9.nt.edit	1	639



Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
57	2829053CB1	1370		170756F1 (BARNOR02)	1	534
				2829053F6 (TLYMNOT03)	428	989
				6098294H1 (UTRENOT09)	849	1143
				5279076H1 (MUSLNOT01)	1071	1308
				4588915H1 (MASTXT01)	1132	1370
58	3068234CB1	1567		7048989V1	1	459
				70488597V1	353	883
				5837294H1 (FTUBTUT01)	730	983
				70490272V1	955	1567
				6035153H1 (PITUNOT06)	1	582
59	5029478CB1	1321		6558521H1 (BRAFNON02)	504	1190
				5076961F6 (COLCTUT03)	742	1321
				5496406H1 (BRABDIR01)	1	250
				1720010F6 (BLADNOT06)	151	708
				6969401U1	602	710
61	2200534CB1	1095	1037-1095, 372-491	5102576F6 (PROSTUS20)	673	1110
				g2905881.v113.gs_2	1	948
				2200534F6 (SPINFET02)	534	1095
				576308R6 (BRAVXT04)	490	1051
				3275821F6 (PROSBPT06)	1	548
62	3275821CB1	1665	1431-1665, 765-1294, 240-597	g3779013.v113.gs_9	265	1665
				2762536H1 (BRSTNOT12)	745	994
				g5578767.v113.gs_4	262	1338
				3744167H1 (THYMNOT08)	693	977
				g835247	1212	1609
63	3744167CB1	1609	1184-1238, 249-522	3474586H1 (LUNGNOT27)	1	309
				g2431610.v113.gs_4.nt	1	945
				g3093312.v113.gs_10.nt	1	1098
				g4190944.v113.gs_3.nt	1	954
				g4467309.v113.gs_2.nt	1	1008
64	7472007CB1	945		g4567182.v113.gs_19.nt	1	930
				g5262456.v113.gs_7.nt	1	711
				g5523795.v113.gs_12.nt	1	1092
65	7472008CB1	1098				
66	7472013CB1	954				
67	7472015CB1	1008				
68	7472016CB1	930				
69	7472017CB1	711				
70	7472018CB1	1092				

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
71	7472019CB1	927		g5566548.v113.gs_7.nt	1	927
72	7472021CB1	1032		g5708153.v113.gs_6.nt	1	1032
73	7472009CB1	972		g3213020.v113.gs_4.nt	1	972
74	7472010CB1	900		g3738097.v113.gs_9.nt	1	900
75	7472011CB1	924		g3924656.v113.gs_5.nt	1	924
76	7472012CB1	945		g4190944.v113.gs_1.nt	1	945
77	7472014CB1	933		g4190944.v113.gs_4.nt	1	933
78	7472020CB1	1080		g5706779.v113.gs_3.nt	1	1080

Table 5

Polynucleotide SEQ ID NO:	Incyte Project ID	Representative Library
61	2200534CB1	BRVVTXT04
62	3275821CB1	PROSBPT06
63	3744167CB1	LUNGNOT27

Table 6

Library	Vector	Library Description
BRAVXT04	PSPORT1	Library was constructed using RNA isolated from separate populations of human astrocytes stimulated for 4 to 6 hours with a combination of cytokines including IL-1. The RNA was pooled for polyA RNA isolation and library construction.
LUNGNOT27	pINCY	Library was constructed using RNA isolated from lung tissue removed from a 17-year-old Hispanic female.
PROSBPT06	pINCY	Library was constructed using RNA isolated from diseased prostate tissue remove from a 66-year-old Caucasian male during a radical prostatectomy and lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated grade 2 (of 4) adenocarcinoma, Gleason grade 3+3. The patient presented with elevated prostate specific antigen (PSA), proteinuria, decreased renal function, and urinary frequency. Patient history included hemiparesis, depressive disorder, sleep apnea, psoriasis, mitral valve prolapse, cerebrovascular disease, benign hypertension, and impotence. Family history included benign hypertension, cerebrovascular disease, and colon cancer.

Table 7

Program	Description	Reference	Parameter Threshold
ABIFACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25:3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. USA 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183:63-98; and Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.0E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S. and J.G. Henikoff (1991) Nucleic Acids Res. 19:6565-6572; Henikoff, J.G. and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Atwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37:417-424.	Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1998) Nucleic Acids Res. 26:320-322; Durbin, R. et al. (1998) Our World View, in a Nutshell, Cambridge Univ. Press, pp. 1-350.	PFAM hits: Probability value= 1.0E-3 or less Signal peptide hits: Score= 0 or greater

Table 7 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, M. et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221.	Normalized quality score > GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M.S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies.	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12:431-439.	Score=3.5 or greater
TMAP	A program that uses weight matrices to delineate transmembrane segments on protein sequences and determine orientation.	Persson, B. and P. Argos (1994) J. Mol. Biol. 237:182-192; Persson, B. and P. Argos (1996) Protein Sci. 5:363-371.	
TMHMMER	A program that uses a hidden Markov model (HMM) to delineate transmembrane segments on protein sequences and determine orientation.	Sonnhammer, E.L. et al. (1998) Proc. Sixth Intl. Conf. on Intelligent Systems for Mol. Biol., Glasgow et al., eds., The Am. Assoc. for Artificial Intelligence Press, Menlo Park, CA, pp. 175-182.	
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

- 5       a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39,  
      b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39,  
      c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and  
10       d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39.

2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1-39.

15

3. An isolated polynucleotide encoding a polypeptide of claim 1.

4. An isolated polynucleotide encoding a polypeptide of claim 2.

20

5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:40-78.

6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

25

7. A cell transformed with a recombinant polynucleotide of claim 6.

8. A transgenic organism comprising a recombinant polynucleotide of claim 6.

30

9. A method for producing a polypeptide of claim 1, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

35

b) recovering the polypeptide so expressed.

10. An isolated antibody which specifically binds to a polypeptide of claim 1.

11. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

- 5       a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78,  
      b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78,  
      c) a polynucleotide sequence complementary to a),  
      d) a polynucleotide sequence complementary to b), and  
10       e) an RNA equivalent of a)-d).

12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 11.

15       13. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

- a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization  
20       complex is formed between said probe and said target polynucleotide or fragments thereof, and  
      b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

25       14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.

      15. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

- a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and  
30       b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

16. A composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

35



17. A composition of claim 16, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-39.

18. A method for treating a disease or condition associated with decreased expression of functional GCREC, comprising administering to a patient in need of such treatment the composition of claim 16.

19. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting agonist activity in the sample.

20. A composition comprising an agonist compound identified by a method of claim 19 and a pharmaceutically acceptable excipient.

21. A method for treating a disease or condition associated with decreased expression of functional GCREC, comprising administering to a patient in need of such treatment a composition of claim 20.

22. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample.

23. A composition comprising an antagonist compound identified by a method of claim 22 and a pharmaceutically acceptable excipient.

24. A method for treating a disease or condition associated with overexpression of functional GCREC, comprising administering to a patient in need of such treatment a composition of claim 23.

25. A method of screening for a compound that specifically binds to the polypeptide of claim 1, said method comprising the steps of:

- a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and
- b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a

compound that specifically binds to the polypeptide of claim 1.

26. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, said method comprising:

- 5       a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,
- b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and
- c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in
- 10       the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.

27. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method

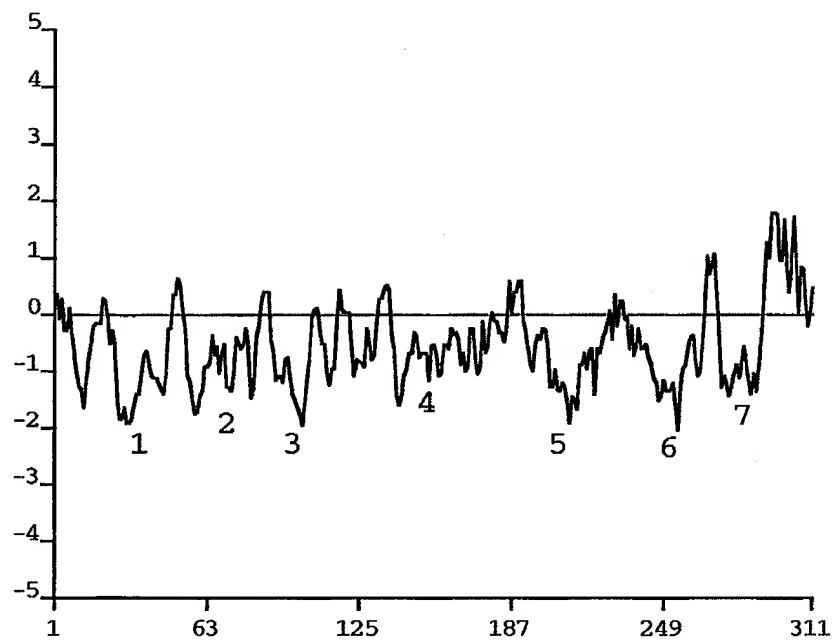
15       comprising:

- a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,
- b) detecting altered expression of the target polynucleotide, and
- c) comparing the expression of the target polynucleotide in the presence of varying amounts of
- 20       the compound and in the absence of the compound.

28. A method for assessing toxicity of a test compound, said method comprising:

- a) treating a biological sample containing nucleic acids with the test compound;
- b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at
- 25       least 20 contiguous nucleotides of a polynucleotide of claim 11 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 11 or fragment thereof;
- c) quantifying the amount of hybridization complex; and
- 30       d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

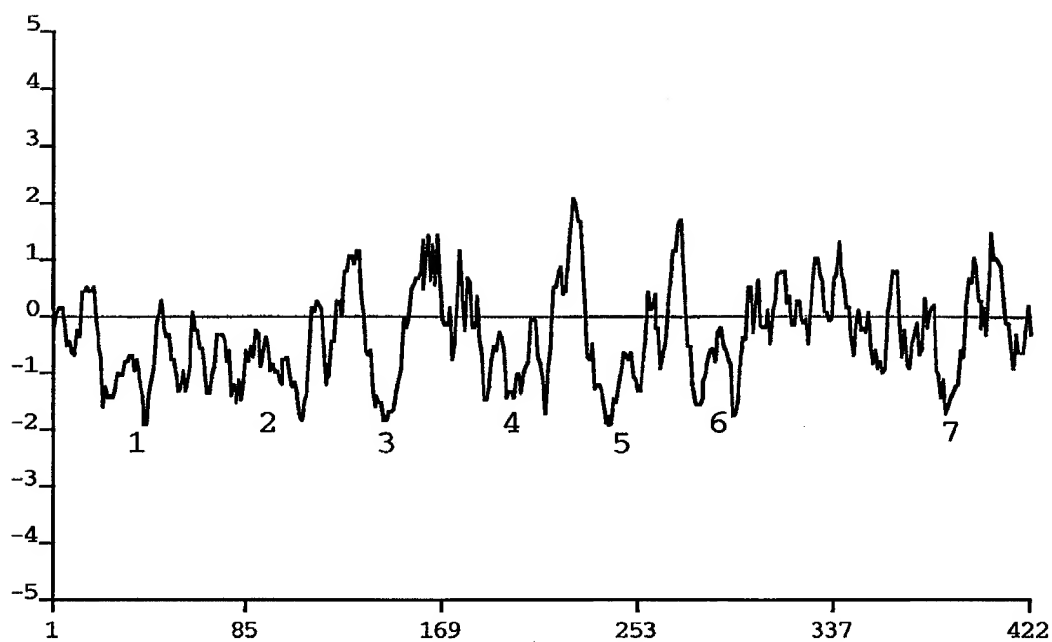
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SEQ ID NO:1  
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FIGURE 1

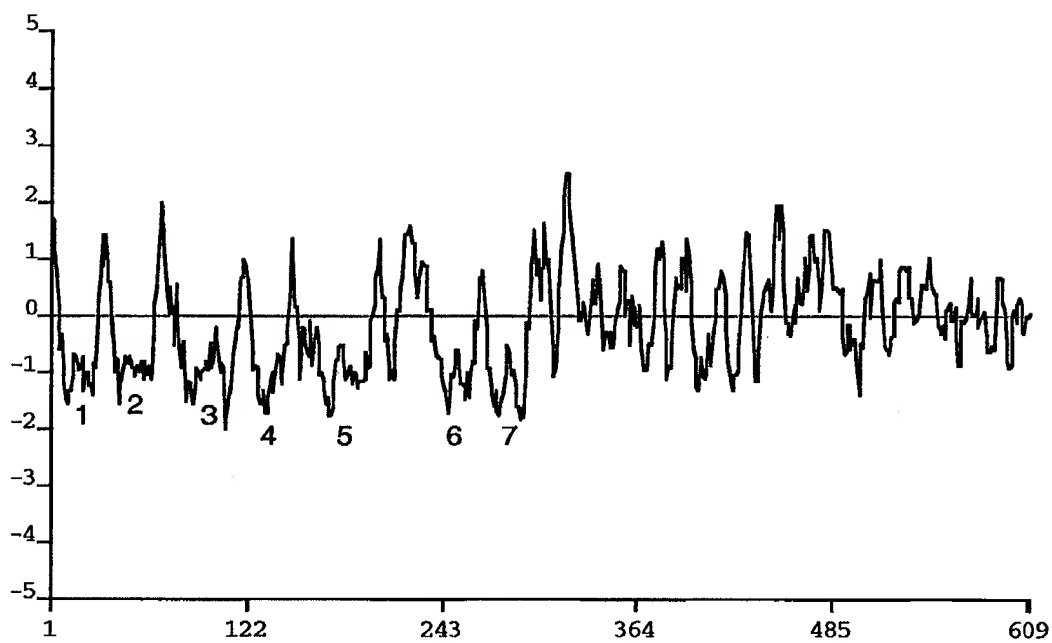
2/9



SEQ ID NO:3  
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FIGURE 2

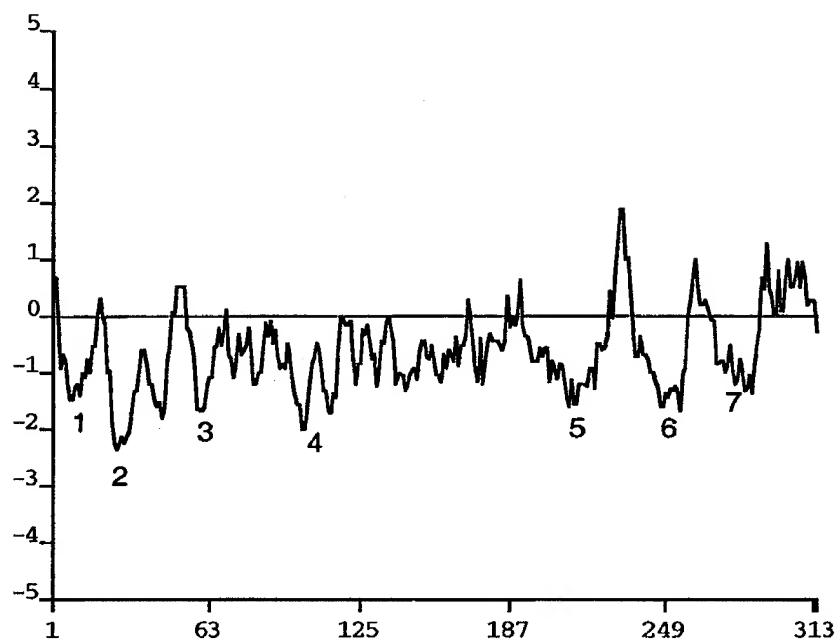
3/9



SEQ ID NO:4  
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FIGURE 3

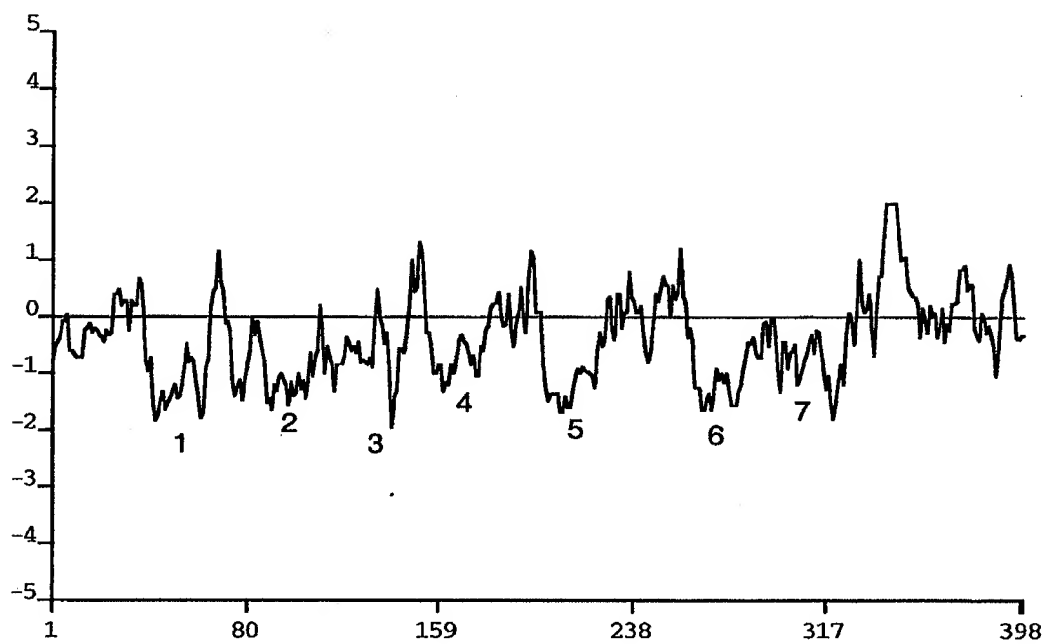
4/9



SEQ ID NO:5  
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FIGURE 4

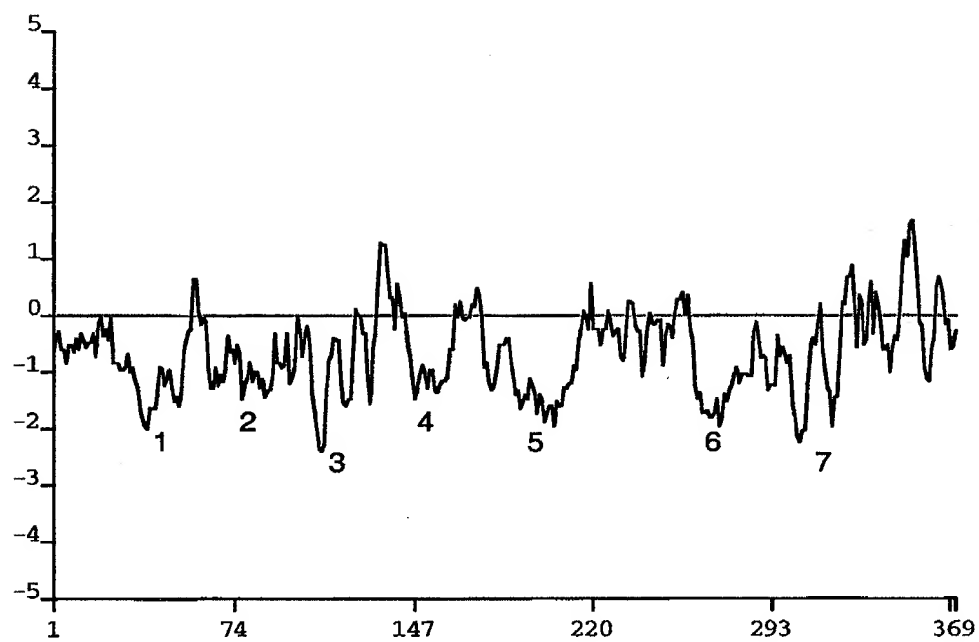
5/9



SEQ ID NO:6  
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FIGURE 5

6/9

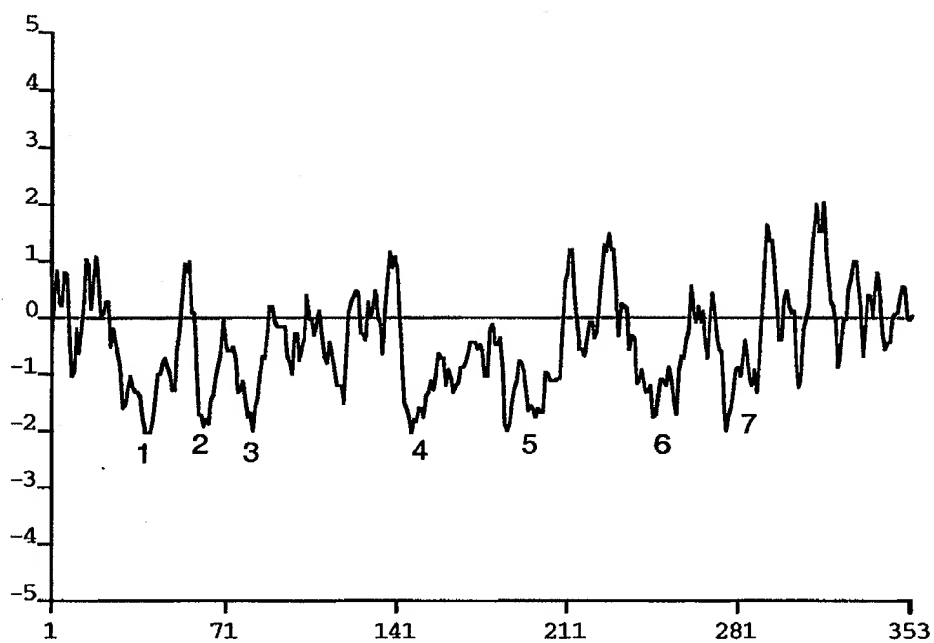


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FIGURE 6



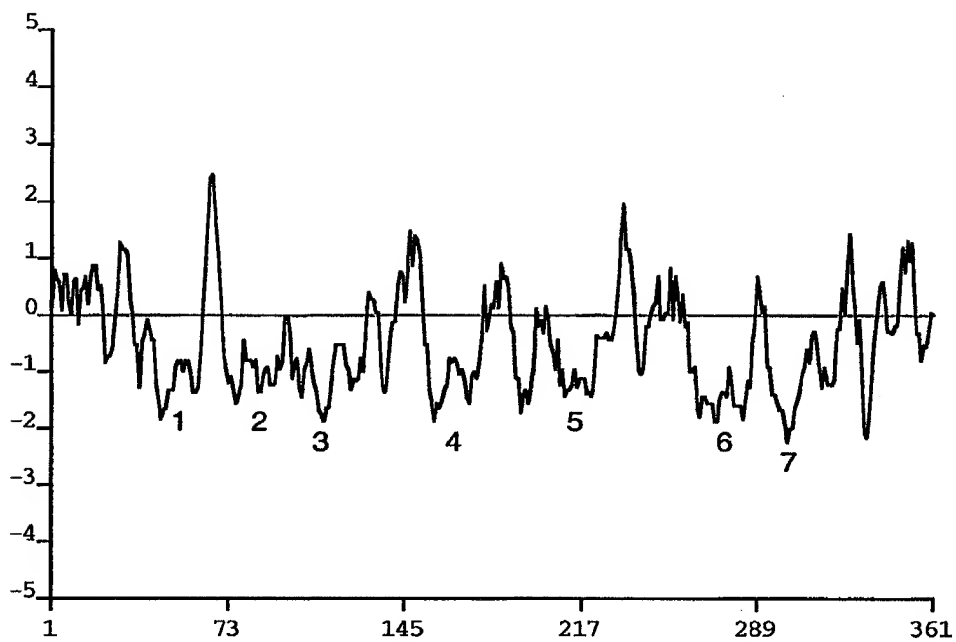
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SEQ ID NO:19  
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FIGURE 7

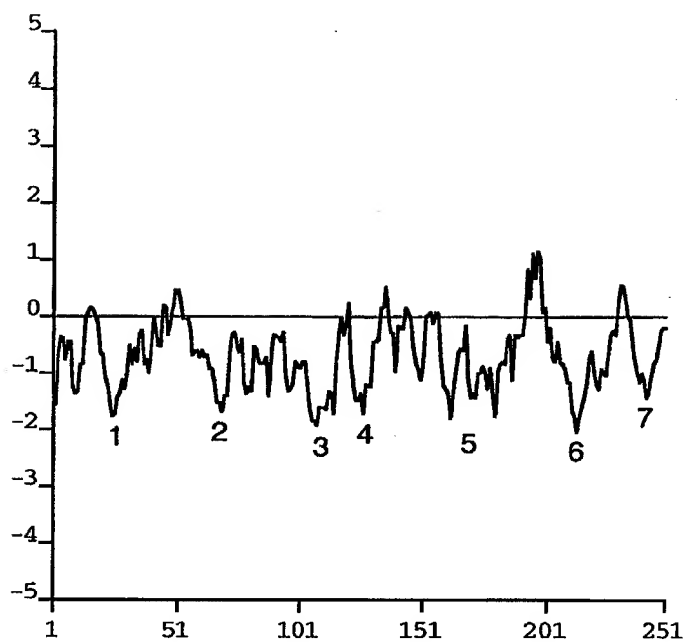
8/9



SEQ ID NO:20  
(Incyte ID No. 5029478CD1)

FIGURE 8

9/9



SEQ ID NO:21  
(Incyte ID No. 5102576CD1)

FIGURE 9

<110> INCYTE GENOMICS, INC.  
 BURFORD, Neil  
 BAUGHN, Mariah R.  
 AU-YOUNG, Janice  
 YANG, Junming  
 LU, Dyung Aina M.  
 REDDY, Roopa

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Arg	Leu	Ser	Phe	Cys	Ala	Ser	His	Ile	Ile	Lys	His	Phe	Phe	Cys	220	225	230	235
Asp	Thr	Gln	Pro	Val	Leu	Lys	Leu	Ser	Cys	Ser	Asp	Thr	Ser	Ser	240	245	250	255
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Ala Ala Met Ser Pro Gly Phe Arg Pro Leu Asn Thr His Ala Ile  
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Ala Leu Ser Val Pro Asp Ser Gln Arg Leu Ser Phe Trp Glu Ala  
365 370 375  
Tyr Arg Val Tyr Thr Gln Glu Gly Gly Leu Gly Thr Trp Thr Phe  
380 385 390  
Gly Trp Gln Phe Gln Leu Ser Asn Ala Glu Glu Tyr Lys Val Trp

	395		400		405
Lys Pro Gly Pro	Arg Glu Gly Ser Ala	Ala Gly Asn Gly Phe	Phe		
	410	415	420		
Lys Leu					

<210> 4  
 <211> 609  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 3291235CD1

<400> 4  
 Met Ser Asp Glu Arg Arg Leu Pro Gly Ser Ala Val Gly Trp Leu  
 1 5 10 15  
 Val Cys Gly Gly Leu Ser Leu Leu Ala Asn Ala Trp Gly Ile Leu  
 20 25 30  
 Ser Val Gly Ala Lys Gln Lys Lys Trp Lys Pro Leu Glu Phe Leu  
 35 40 45  
 Leu Cys Thr Leu Ala Ala Thr His Met Leu Asn Val Ala Val Pro  
 50 55 60  
 Ile Ala Thr Tyr Ser Val Val Gln Leu Arg Arg Gln Arg Pro Asp  
 65 70 75  
 Phe Glu Trp Asn Glu Gly Leu Cys Lys Val Phe Val Ser Thr Phe  
 80 85 90  
 Tyr Thr Leu Thr Leu Ala Thr Cys Phe Ser Val Thr Ser Leu Ser  
 95 100 105  
 Tyr His Arg Met Trp Met Val Cys Trp Pro Val Asn Tyr Arg Leu  
 110 115 120  
 Ser Asn Ala Lys Lys Gln Ala Val His Thr Val Met Gly Ile Trp  
 125 130 135  
 Met Val Ser Phe Ile Leu Ser Ala Leu Pro Ala Val Gly Trp His  
 140 145 150  
 Asp Thr Ser Glu Arg Phe Tyr Thr His Gly Cys Arg Phe Ile Val  
 155 160 165  
 Ala Glu Ile Gly Leu Gly Phe Gly Val Cys Phe Leu Leu Leu Val  
 170 175 180  
 Gly Gly Ser Val Ala Met Gly Val Ile Cys Thr Ala Ile Ala Leu  
 185 190 195  
 Phe Gln Thr Leu Ala Val Gln Val Gly Arg Gln Ala Asp His Arg  
 200 205 210  
 Ala Phe Thr Val Pro Thr Ile Val Val Glu Asp Ala Gln Gly Lys  
 215 220 225  
 Arg Arg Ser Ser Ile Asp Gly Ser Glu Pro Ala Lys Thr Ser Leu  
 230 235 240  
 Gln Thr Thr Gly Leu Val Thr Thr Ile Val Phe Ile Tyr Asp Cys  
 245 250 255  
 Leu Met Gly Phe Pro Val Leu Val Val Ser Phe Ser Ser Leu Arg  
 260 265 270  
 Ala Asp Ala Ser Ala Pro Trp Met Ala Leu Cys Val Leu Trp Cys  
 275 280 285  
 Ser Val Ala Gln Ala Leu Leu Leu Pro Val Phe Leu Trp Ala Cys  
 290 295 300  
 Asp Arg Tyr Arg Ala Asp Leu Lys Ala Val Arg Glu Lys Cys Met  
 305 310 315  
 Ala Leu Met Ala Asn Asp Glu Glu Ser Asp Asp Glu Thr Ser Leu  
 320 325 330  
 Glu Gly Gly Ile Ser Pro Asp Leu Val Leu Glu Arg Ser Leu Asp  
 335 340 345  
 Tyr Gly Tyr Gly Gly Asp Phe Val Ala Leu Asp Arg Met Ala Lys  
 350 355 360  
 Tyr Glu Ile Ser Ala Leu Glu Gly Gly Leu Pro Gln Leu Tyr Pro  
 365 370 375  
 Leu Arg Pro Leu Gln Glu Asp Lys Met Gln Tyr Leu Gln Val Pro



Pro Thr Arg Arg	380	385	390
Phe Ser His Asp Asp	395	Ala Asp Val Trp Ala	Ala
Val Pro Leu Pro	410	400	405
Ala Phe Leu Pro Arg	415	Trp Gly Ser Gly Lys	Asp
Leu Ser Ala Leu	425	415	420
Ala His Leu Val Leu	430	Pro Ala Gly Pro Glu	Arg
Pro Arg Ala Ser	440	430	435
Leu Leu Ala Phe Ala	445	Glu Asp Ala Pro Leu	Ser
Arg Ala Arg Arg	455	445	450
Arg Ser Ala Glu Ser	460	Leu Leu Ser Leu Arg	Pro
Ser Ala Val Asp	470	460	465
Ser Gly Pro Arg Gly	475	Ala Arg Asp Ser Pro	Pro
Gly Ser Pro Arg	485	475	480
Arg Arg Pro Gly Pro	490	Gly Pro Arg Ser Ala	Ser
Ala Ser Leu Leu	500	490	495
Pro Asp Ala Phe Ala	505	Leu Thr Ala Phe Glu	Cys
Glu Pro Gln Ala	515	505	510
Leu Arg Arg Pro Pro	520	Gly Pro Phe Pro Ala	Ala
Pro Ala Ala Pro	530	520	525
Asp Gly Ala Asp Pro	535	Gly Glu Ala Pro Thr	Pro
Pro Ser Ser Ala	545	535	540
Gln Arg Ser Pro Gly	550	Pro Arg Pro Ser Ala	His
Ser His Ala Gly	560	550	555
Ser Leu Arg Pro Gly	565	Leu Ser Ala Ser Trp	Gly
Glu Pro Gly Gly	575	565	570
Leu Arg Ala Ala Gly	580	Gly Gly Gly Ser Thr	Ser
Ser Phe Leu Ser	590	580	585
Ser Pro Ser Glu Ser	595	Ser Gly Tyr Ala Thr	Leu
His Ser Asp Ser	605	595	600
Leu Gly Ser Ala Ser			

<210> 5  
 <211> 313  
 <212> PRT  
 <213> Homo sapiens

<220>  
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 <223> Incyte ID No: 7472001CD1

<400> 5

Met Glu Arg Ile Asn	5	Ser Thr Leu Leu Thr	10	Ala Phe Ile Leu Thr	15
Gly Ile Pro Tyr Pro	20	Leu Arg Leu Arg Thr	25	Leu Phe Phe Val Phe	30
Phe Phe Leu Ile Tyr	35	Ile Leu Thr Gln Leu	40	Gly Asn Leu Leu Ile	45
Leu Ile Thr Val Trp	50	Ala Asp Pro Arg Leu	55	His Ala Arg Pro Met	60
Tyr Ile Phe Leu Gly	65	Val Leu Ser Val Ile	70	Asp Met Ser Ile Ser	75
Ser Ile Ile Val Pro	80	Arg Leu Met Met Asn	85	Phe Thr Leu Gly Val	90
Lys Pro Ile Pro Phe	95	Gly Gly Cys Val Ala	100	Gln Leu Tyr Phe Tyr	105
His Phe Leu Gly Ser	110	Thr Gln Cys Phe Leu	115	Tyr Thr Leu Met Ala	120
Tyr Asp Arg Tyr Leu	125	Ala Ile Cys Gln Pro	130	Leu Arg Tyr Pro Val	135
Leu Met Thr Ala Lys	140	Leu Ser Ala Leu Leu	145	Val Ala Gly Ala Trp	150
Met Ala Gly Ser Ile	155	His Gly Ala Leu Gln	160	Ala Ile Leu Thr Phe	165
Arg Leu Pro Tyr Cys	170	Gly Pro Asn Gln Val	175	Asp Tyr Phe Phe Cys	180
Asp Ile Pro Ala Val		Leu Arg Leu Ala Cys		Ala Asp Thr Thr Val	

Asn	Glu	Leu	Val	Thr	Phe	Val	Asp	Ile	Gly	Val	Val	Val	Ala	Ser	185	190	195
															200	205	210
Cys	Phe	Ser	Leu	Ile	Leu	Leu	Ser	Tyr	Ile	Gln	Ile	Ile	Gln	Ala	215	220	225
Ile	Leu	Arg	Ile	His	Thr	Ala	Asp	Gly	Arg	Arg	Arg	Ala	Phe	Ser	230	235	240
Thr	Cys	Gly	Ala	His	Val	Thr	Val	Val	Thr	Val	Tyr	Tyr	Val	Pro	245	250	255
Cys	Ala	Phe	Ile	Tyr	Leu	Arg	Pro	Glu	Thr	Asn	Ser	Pro	Leu	Asp	260	265	270
Gly	Ala	Ala	Ala	Leu	Val	Pro	Thr	Ala	Ile	Thr	Pro	Phe	Leu	Asn	275	280	285
Pro	Leu	Ile	Tyr	Thr	Leu	Arg	Asn	Gln	Glu	Val	Lys	Leu	Ala	Leu	290	295	300
Lys	Arg	Met	Leu	Arg	Ser	Pro	Arg	Thr	Pro	Ser	Glu	Val			305	310	

&lt;210&gt; 6

&lt;211&gt; 398

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472003CD1

&lt;400&gt; 6

Met	His	Thr	Val	Ala	Thr	Ser	Gly	Pro	Asn	Ala	Ser	Trp	Gly	Ala	1	5	10	15
Pro	Ala	Asn	Ala	Ser	Gly	Cys	Pro	Gly	Cys	Gly	Ala	Asn	Ala	Ser	20	25	30	35
Asp	Gly	Pro	Val	Pro	Ser	Pro	Arg	Ala	Val	Asp	Ala	Trp	Leu	Val	35	40	45	50
Pro	Leu	Phe	Phe	Ala	Ala	Leu	Met	Leu	Leu	Gly	Leu	Val	Gly	Asn	50	55	60	65
Ser	Leu	Val	Ile	Tyr	Val	Ile	Cys	Arg	His	Lys	Pro	Met	Arg	Thr	65	70	75	80
Val	Thr	Asn	Phe	Tyr	Ile	Ala	Asn	Leu	Ala	Ala	Thr	Asp	Val	Thr	80	85	90	95
Phe	Leu	Leu	Cys	Cys	Val	Pro	Phe	Thr	Ala	Leu	Leu	Tyr	Pro	Leu	95	100	105	110
Pro	Gly	Trp	Val	Leu	Gly	Asp	Phe	Met	Cys	Lys	Phe	Val	Asn	Tyr	110	115	120	125
Ile	Gln	Gln	Val	Ser	Val	Gln	Ala	Thr	Cys	Ala	Thr	Leu	Thr	Ala	125	130	135	140
Met	Ser	Val	Asp	Arg	Trp	Tyr	Val	Thr	Val	Phe	Pro	Leu	Arg	Ala	140	145	150	155
Leu	His	Arg	Arg	Thr	Pro	Arg	Leu	Ala	Leu	Ala	Val	Ser	Leu	Ser	155	160	165	170
Ile	Trp	Thr	Gly	Ser	Ala	Ala	Val	Ser	Ala	Pro	Val	Leu	Ala	Leu	170	175	180	185
His	Arg	Leu	Ser	Pro	Gly	Pro	Arg	Ala	Tyr	Cys	Ser	Glu	Ala	Phe	185	190	195	200
Pro	Ser	Arg	Ala	Leu	Glu	Arg	Ala	Phe	Ala	Leu	Tyr	Asn	Leu	Leu	200	205	210	215
Ala	Leu	Tyr	Leu	Leu	Pro	Leu	Leu	Ala	Thr	Cys	Ala	Cys	Tyr	Ala	215	220	225	230
Ala	Met	Leu	Arg	His	Leu	Gly	Arg	Val	Ala	Val	Arg	Pro	Ala	Pro	230	235	240	245
Ala	Asp	Ser	Ala	Leu	Gln	Gly	Gln	Val	Leu	Ala	Glu	Arg	Ala	Gly	245	250	255	260
Ala	Val	Arg	Ala	Lys	Val	Ser	Arg	Leu	Val	Ala	Ala	Val	Val	Leu	260	265	270	275
Leu	Phe	Ala	Ala	Cys	Trp	Gly	Pro	Ile	Gln	Leu	Phe	Leu	Val	Leu	275	280	285	290
Gln	Ala	Leu	Gly	Pro	Ala	Gly	Ser	Trp	His	Pro	Arg	Ser	Tyr	Ala	290	295	300	305

Ala Tyr Ala Leu	290	Thr Trp Ala His	295	Cys Met Ser Tyr Ser	300
	305		310		315
Ser Ala Leu Asn	320	Leu Leu Tyr Ala	325	Phe Leu Gly Ser His	330
	335		340		345
Arg Gln Ala Phe	350	Arg Val Cys Pro	355	Cys Ala Pro Arg Arg	360
	365		370		375
Arg Arg Pro Arg	380	Arg Pro Gly Pro Ser	385	Asp Pro Ala Ala Pro	390
	395				
Ala Glu Leu Leu		Arg Leu Gly Ser His		Pro Ala Pro Ala Arg	
Gln Lys Pro Gly		Ser Ser Gly Leu Ala		Ala Arg Gly Leu Cys	
Leu Gly Glu Asp		Asn Ala Pro Leu			

&lt;210&gt; 7

&lt;211&gt; 369

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472004CD1

&lt;400&gt; 7

Met Ala Pro Thr	Gly	Leu Ser Ser Leu	Thr	Val Asn Ser Thr	Ala
1	5		10		15
Val Pro Thr Thr	Pro	Ala Ala Phe Lys	Ser	Leu Asn Leu Pro	Leu
	20		25		30
Gln Ile Thr Leu	Ser	Ala Ile Met Ile	Phe	Ile Leu Phe Val	Ser
	35		40		45
Phe Leu Gly Asn	Leu	Val Val Cys Leu	Met	Val Tyr Gln Lys	Ala
	50		55		60
Ala Met Arg Ser	Ala	Ile Asn Ile Leu	Leu	Ala Ser Leu Ala	Phe
	65		70		75
Ala Asp Met Leu	Leu	Ala Val Leu Asn	Met	Pro Phe Ala Leu	Val
	80		85		90
Thr Ile Leu Thr	Thr	Arg Trp Ile Phe	Gly	Lys Phe Phe Cys	Arg
	95		100		105
Val Ser Ala Met	Phe	Trp Leu Phe	Val	Ile Glu Gly Val	Ala
	110		115		120
Ile Leu Leu Ile	Ile	Ser Ile Asp Arg	Phe	Leu Ile Ile Val	Gln
	125		130		135
Arg Gln Asp Lys	Leu	Asn Pro Tyr Arg	Ala	Lys Val Leu Ile	Ala
	140		145		150
Val Ser Trp Ala	Thr	Ser Phe Cys Val	Ala	Phe Pro Leu Ala	Val
	155		160		165
Gly Asn Pro Asp	Leu	Gln Ile Pro Ser	Arg	Ala Pro Gln Cys	Val
	170		175		180
Phe Gly Tyr Thr	Thr	Asn Pro Gly Tyr	Gln	Ala Tyr Val Ile	Leu
	185		190		195
Ile Ser Leu Ile	Ser	Phe Phe Ile Pro	Phe	Leu Val Ile Leu	Tyr
	200		205		210
Ser Phe Met Gly	Ile	Leu Asn Thr Leu	Arg	His Asn Ala Leu	Arg
	215		220		225
Ile His Ser Tyr	Pro	Glu Gly Ile Cys	Leu	Ser Gln Ala Ser	Lys
	230		235		240
Leu Gly Leu Met	Ser	Leu Gln Arg Pro	Phe	Gln Met Ser Ile	Asp
	245		250		255
Met Gly Phe Lys	Thr	Arg Ala Phe Thr	Thr	Ile Leu Ile Leu	Phe
	260		265		270
Ala Val Phe Ile	Val	Cys Trp Ala Pro	Phe	Thr Thr Tyr Ser	Leu
	275		280		285
Val Ala Thr Phe	Ser	Lys His Phe Tyr	Tyr	Gln His Asn Phe	Phe
	290		295		300
Glu Ile Ser Thr	Trp	Leu Leu Trp Leu	Cys	Tyr Leu Lys Ser	Ala

Leu Asn Pro Leu	305	Tyr Tyr Trp Arg	310	Ile Lys Lys Phe His	315
	320		325		330
Ala Cys Leu Asp Met	335	Met Pro Lys Ser	340	Phe Lys Phe Leu Pro	345
Leu Pro Gly His Thr	350	Lys Arg Arg Ile	355	Arg Pro Ser Ala Val	360
Val Cys Gly Glu His	365	Arg Thr Val Val			

<210> 8  
 <211> 194  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7475687CP1

Met Ala Tyr Asp Arg	1	Tyr Leu Ala Ile Cys	10	Gln Pro Leu Arg Tyr	15
Pro Val Leu Met Asn	20	Gly Arg Leu Cys Thr	25	Val Leu Val Ala Gly	30
Ala Trp Val Ala Gly	35	Ser Met His Gly Ser	40	Ile Gln Ala Thr Leu	45
Thr Phe Arg Leu Pro	50	Tyr Cys Gly Pro Asn	55	Gln Val Asp Tyr Phe	60
Ile Cys Asp Ile Pro	65	Ala Val Leu Arg Leu	70	Ala Cys Ala Asp Thr	75
Thr Val Asn Glu Leu	80	Val Thr Phe Val Asp	85	Ile Gly Val Val Ala	90
Ala Ser Cys Phe Met	95	Leu Ile Leu Leu Ser	100	Tyr Ala Asn Ile Val	105
Asn Ala Ile Leu Lys	110	Ile Arg Thr Thr Asp	115	Gly Arg Arg Arg Ala	120
Phe Ser Thr Cys Gly	125	Ser His Leu Ile Val	130	Val Thr Val Tyr Tyr	135
Val Pro Cys Ile Phe	140	Ile Tyr Leu Arg Ala	145	Gly Ser Lys Gly Pro	150
Leu Asp Gly Ala Ala	155	Ala Val Phe Tyr Thr	160	Val Val Thr Pro Leu	165
Leu Asn Pro Leu Ile	170	Tyr Thr Leu Arg Asn	175	Gln Glu Val Lys Ser	180
Ala Leu Lys Arg Ile	185	Thr Ala Gly Gln Ala	190	Asp Val Asn Asn	

<210> 9  
 <211> 173  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7483029CP1

Met Tyr Leu Val Thr	1	Val Leu Gly Asn Leu	10	Leu Ile Ile Leu Ala	15
Thr Ile Ser Asp Ser	20	His Leu His Thr Pro	25	Met Tyr Phe Phe Leu	30
Ser Asn Leu Ser Phe	35	Ala Asp Ile Cys Phe	40	Val Ser Thr Thr Val	45
Pro Lys Met Leu Val	50	Asn Ile Gln Thr Gln	55	Ser Arg Val Ile Thr	60
Tyr Ala Asp Cys Ile	65	Thr Gln Met Cys Phe	70	Phe Ile Leu Phe Val	75

Val	Leu	Asp	Ser	Leu	Leu	Leu	Thr	Val	Met	Ala	Tyr	Asp	Arg	Phe	
				80					85					90	
Val	Ala	Ile	Cys	His	Pro	Leu	His	Tyr	Thr	Val	Ile	Met	Asn	Ser	
				95					100					105	
Trp	Leu	Cys	Gly	Leu	Leu	Val	Leu	Val	Ser	Trp	Ile	Val	Ser	Ile	
				110					115					120	
Leu	Tyr	Ser	Leu	Leu	Gln	Ser	Ile	Met	Ala	Leu	Gln	Leu	Ser	Phe	
				125					130					135	
Cys	Thr	Glu	Leu	Lys	Ile	Pro	His	Phe	Phe	Cys	Glu	Leu	Asn	Gln	
				140					145					150	
Val	Ile	His	Leu	Ala	Cys	Ser	Asp	Thr	Phe	Ile	Asn	Asp	Met	Met	
				155					160					165	
Met	Asn	Phe	Thr	Ser	Val	Leu	Leu								
				170											

<210> 10  
 <211> 220  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7477933CP1

Pro	Met	Tyr	Phe	Phe	Leu	Ser	Asn	Leu	Cys	Trp	Ala	Asp	Ile	Gly	
1				5					10					15	
Leu	Thr	Ser	Ala	Thr	Val	Pro	Lys	Val	Ile	Leu	Asp	Met	Gln	Ser	
				20					25					30	
His	Ser	Arg	Val	Ile	Ser	His	Val	Gly	Cys	Leu	Thr	Gln	Met	Ser	
				35					40					45	
Phe	Leu	Val	Leu	Phe	Ala	Cys	Ile	Glu	Gly	Met	Leu	Leu	Thr	Val	
				50					55					60	
Met	Ala	Tyr	Gly	Cys	Phe	Val	Ala	Ile	Cys	Arg	Pro	Leu	His	Tyr	
				65					70					75	
Pro	Val	Ile	Val	Asn	Pro	His	Leu	Cys	Val	Phe	Phe	Val	Leu	Val	
				80					85					90	
Ser	Phe	Phe	Leu	Asn	Leu	Leu	Asp	Ser	Gln	Leu	His	Ser	Trp	Ile	
				95					100					105	
Val	Leu	Gln	Phe	Thr	Ile	Ile	Lys	Asn	Val	Glu	Ile	Ser	Asn	Phe	
				110					115					120	
Phe	Cys	Asp	Pro	Ser	Gln	Leu	Leu	Asn	Leu	Ala	Cys	Ser	Asp	Ser	
				125					130					135	
Val	Ile	Asn	Ser	Ile	Phe	Ile	Tyr	Phe	Asp	Ser	Thr	Met	Phe	Gly	
				140					145					150	
Phe	Leu	Pro	Ile	Ser	Gly	Ile	Leu	Leu	Ser	Tyr	Tyr	Lys	Ile	Val	
				155					160					165	
Pro	Ser	Ile	Leu	Arg	Met	Ser	Ser	Ser	Asp	Gly	Lys	Tyr	Lys	Ala	
				170					175					180	
Phe	Ser	Thr	Tyr	Gly	Ser	His	Leu	Gly	Val	Val	Cys	Trp	Phe	Tyr	
				185					190					195	
Gly	Thr	Val	Ile	Gly	Met	Tyr	Leu	Ala	Ser	Ala	Val	Ser	Pro	Pro	
				200					205					210	
Pro	Arg	Asn	Gly	Val	Val	Ala	Ser	Val	Met						
				215					220						

<210> 11  
 <211> 302  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7475164CP1

<400> 11  
 Ala Glu Phe Ile Leu Ala Gly Leu Thr Gln Arg Pro Glu Leu Gln

1	5	10	15
Leu Pro Leu Phe Leu	Leu Phe Leu Gly Ile	Tyr Val Val Thr Val	
20	25	30	
Val Gly Asn Leu Gly	Met Ile Phe Leu Ile	Ala Leu Ser Ser Gln	
35	40	45	
Leu Tyr Pro Pro Val	Tyr Tyr Phe Leu Ser	His Leu Ser Phe Ile	
50	55	60	
Asp Leu Cys Tyr Ser	Ser Val Ile Thr Pro	Lys Met Leu Val Asn	
65	70	75	
Phe Val Pro Glu Glu	Asn Ile Ile Ser Phe	Leu Glu Cys Ile Thr	
80	85	90	
Gln Leu Tyr Phe Phe	Leu Ile Phe Val Ile	Ala Glu Gly Tyr Leu	
95	100	105	
Leu Thr Ala Met Glu	Tyr Asp Arg Tyr Val	Ala Ile Cys Arg Pro	
110	115	120	
Leu Leu Tyr Asn Ile	Val Met Ser His Arg	Val Cys Ser Ile Met	
125	130	135	
Met Ala Val Val Tyr	Ser Leu Gly Phe Leu	Trp Ala Thr Val His	
140	145	150	
Thr Thr Arg Met Ser	Val Leu Ser Phe Cys	Arg Ser His Thr Val	
155	160	165	
Ser His Tyr Phe Cys	Asp Ile Leu Pro Leu	Leu Thr Leu Ser Cys	
170	175	180	
Ser Ser Thr His Ile	Asn Glu Ile Leu Leu	Phe Ile Ile Gly Gly	
185	190	195	
Val Asn Thr Leu Ala	Thr Thr Leu Ala Val	Leu Ile Ser Tyr Ala	
200	205	210	
Phe Ile Phe Ser Ser	Ile Leu Gly Ile His	Ser Thr Glu Gly Gln	
215	220	225	
Ser Lys Ala Phe Gly	Thr Cys Ser Ser His	Leu Leu Ala Val Gly	
230	235	240	
Ile Phe Phe Gly Ser	Ile Thr Phe Met Tyr	Phe Lys Pro Pro Ser	
245	250	255	
Ser Thr Thr Met Glu	Lys Glu Lys Val Ser	Ser Val Phe Tyr Ile	
260	265	270	
Thr Ile Ile Pro Met	Leu Asn Pro Leu Ile	Tyr Ser Leu Arg Asn	
275	280	285	
Lys Asp Val Lys Asn	Ala Leu Lys Lys Met	Thr Arg Gly Arg Gln	
290	295	300	
Ser Ser			

<210> 12  
 <211> 110  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7473909CP1

<400> 12
Gly Pro Arg Thr Ala Ser Gly Cys Val Ile Met Ile Cys Phe Ala
1 5 10 15
Leu Thr Val Leu Ser Tyr Ile Arg Ile Leu Ala Thr Val Val Gln
20 25 30
Ile Arg Ser Ala Ala Ser Arg Arg Lys Ala Phe Ser Thr Cys Ser
35 40 45
Ser His Leu Gly Met Val Leu Leu Phe Tyr Gly Thr Gly Ser Ser
50 55 60
Thr Tyr Met Arg Pro Thr Thr Arg Tyr Ser Pro Leu Glu Gly Arg
65 70 75
Leu Ala Ala Val Phe Tyr Ser Ile Leu Ile Pro Thr Leu Asn Pro
80 85 90
Leu Ile Tyr Ser Leu Arg Asn Gln Asp Met Lys Arg Ala Leu Trp
95 100 105
Lys Leu Tyr Leu Gln

110

<210> 13  
 <211> 178  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7475252CP1

<400> 13  
 Glu Pro Glu Asn Leu Thr Gly Val Leu Glu Phe Leu Leu Leu Gly  
 1 5 10 15  
 Leu Pro Asp Asp Pro Glu Leu Gln Pro Val Leu Phe Gly Leu Phe  
 20 25 30  
 Leu Ser Met Tyr Leu Val Met Val Leu Gly Asn Leu Leu Ile Ile  
 35 40 45  
 Leu Ala Val Ser Ser Asp Ser His Leu His Ser Pro Met Tyr Phe  
 50 55 60  
 Phe Leu Ser Asn Leu Ser Leu Ala Asp Ile Gly Phe Ala Ser Thr  
 65 70 75  
 Thr Val Pro Lys Met Ile Val Asp Ile Gln Ala His Ser Arg Leu  
 80 85 90  
 Ile Ser Tyr Val Gly Cys Leu Thr Gln Met Ser Phe Leu Ile Phe  
 95 100 105  
 Phe Ala Cys Met Glu Ser Leu Leu Leu Ile Val Met Ala Tyr Asp  
 110 115 120  
 Arg Phe Val Ala Ile Cys His Pro Leu His Tyr Gln Val Ile Met  
 125 130 135  
 Ser Pro Arg Leu Cys Gly Phe Leu Val Leu Val Ser Phe Phe Leu  
 140 145 150  
 Ser Leu Leu Asp Ser Gln Leu His Asn Leu Ile Val Leu Gln Leu  
 155 160 165  
 Thr Cys Phe Asn Asp Val Glu Ile Ser Asn Phe Phe Leu  
 170 175

<210> 14  
 <211> 92  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7927572CP1

<400> 14  
 Leu Leu Asp Ala Gln Leu Tyr Asn Leu Ile Ala Leu Gln Met Thr  
 1 5 10 15  
 Cys Phe Lys Asp Val Glu Ile Pro Asn Phe Phe Cys Asp Pro Ser  
 20 25 30  
 Gln Leu Pro His Leu Ala Cys Cys Asp Thr Phe Asn Asn Asn Ile  
 35 40 45  
 Ile Leu Tyr Phe Pro Asp Ala Ile Phe Gly Phe Leu Pro Ile Ser  
 50 55 60  
 Gly Thr Leu Phe Ser Tyr Asp Lys Ile Val Ser Ser Ile Leu Arg  
 65 70 75  
 Val Ser Ser Ser Gly Gly Lys Tyr Lys Ala Phe Ser Thr Tyr Gly  
 80 85 90  
 Ser His

<210> 15  
 <211> 97  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7481257CP1

<400> 15  
 Met Glu Val Thr Thr Phe Ala Met Cys Leu Ile Ile Val Leu Val  
 1 5 10 15  
 Pro Leu Leu Leu Ile Leu Val Ser Tyr Gly Phe Ile Ala Val Ala  
 20 25 30  
 Val Leu Lys Ile Lys Ser Ala Ala Gly Arg Gln Lys Ala Phe Gly  
 35 40 45  
 Thr Cys Ser Ser His Leu Val Val Val Ser Ile Phe Cys Gly Thr  
 50 55 60  
 Val Thr Tyr Met Tyr Ile Gln Pro Gly Asn Ser Pro Asn Gln Asn  
 65 70 75  
 Glu Gly Lys Leu Leu Ser Ile Phe Tyr Ser Ile Val Thr Pro Ser  
 80 85 90  
 Leu Asn Pro Leu Ile Tyr Thr  
 95

<210> 16  
 <211> 133  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7485790CP1

<400> 16  
 Asp Pro Glu Leu Gln Pro Ile Leu Ala Gly Leu Ser Leu Ser Met  
 1 5 10 15  
 Tyr Leu Val Thr Val Leu Arg Asn Leu Leu Ile Ser Leu Ala Val  
 20 25 30  
 Ser Ser Asp Ser His Leu His Thr Pro Met Cys Phe Phe Leu Ser  
 35 40 45  
 Asn Leu Cys Trp Ala Asp Ile Gly Phe Thr Ser Ala Thr Val Pro  
 50 55 60  
 Lys Met Ile Val Asp Met Arg Ser His Ser Gly Val Ile Ser Tyr  
 65 70 75  
 Ala Asp Cys Leu Thr Arg Met Ser Phe Leu Val Leu Phe Ala Cys  
 80 85 90  
 Val Glu Asp Met Leu Leu Thr Val Met Ala Tyr Asp Cys Phe Val  
 95 100 105  
 Ala Ile Cys Arg Pro Leu His Tyr Pro Val Ile Val Asn Pro His  
 110 115 120  
 Leu Cys Val Phe Leu Val Ser Val Ser Phe Ser Leu Ala  
 125 130

<210> 17  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7482993CP1

<400> 17  
 Gly Ser Glu Cys Leu Leu Leu Ala Ala Met Ala Tyr Asp Arg Tyr  
 1 5 10 15  
 Ile Ala Ile Cys Asn Pro Leu Arg Tyr Ser Val Ile Leu Ser Lys  
 20 25 30  
 Val Leu Cys Asn Gln Leu Ala Ala Ser Cys Trp Ala Ala Gly Phe  
 35 40 45  
 Leu Asn Ser Val Val His Thr Val Leu Thr Phe Cys Leu Pro Phe  
 50 55 60



**PCT/US00/33382**

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<210> 18
<211> 180
<212> PRT
<213> Homo sapiens
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<400> 18

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<210> 19
<211> 353
<212> PRT
<213> Homo sapiens
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14/48

&lt;400&gt; 19

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Met Asn Glu Cys His Tyr Asp Lys His Met Asp Phe Phe Tyr Asn
1      5      10      15
Arg Ser Asn Thr Asp Thr Val Asp Asp Trp Thr Gly Thr Lys Leu
20      25      30
Val Ile Val Leu Cys Val Gly Thr Phe Phe Cys Leu Phe Ile Phe
35      40      45
Phe Ser Asn Ser Leu Val Ile Ala Ala Val Ile Lys Asn Arg Lys
50      55      60
Phe His Phe Pro Phe Tyr Tyr Leu Leu Ala Asn Leu Ala Ala Ala
65      70      75
Asp Phe Phe Ala Gly Ile Ala Tyr Val Phe Leu Met Phe Asn Thr
80      85      90
Gly Pro Val Ser Lys Thr Leu Thr Val Asn Arg Trp Phe Leu Arg
95      100      105
Gln Gly Leu Leu Asp Ser Ser Leu Thr Ala Ser Leu Thr Asn Leu
110      115      120
Leu Val Ile Ala Val Glu Arg His Met Ser Ile Met Arg Met Arg
125      130      135
Val His Ser Asn Leu Thr Lys Lys Arg Val Thr Leu Leu Ile Leu
140      145      150
Leu Val Trp Ala Ile Ala Ile Phe Met Gly Ala Val Pro Thr Leu
155      160      165
Gly Trp Asn Cys Leu Cys Asn Ile Ser Ala Cys Ser Ser Leu Ala
170      175      180
Pro Ile Tyr Ser Arg Ser Tyr Leu Val Phe Trp Thr Val Ser Asn
185      190      195
Leu Met Ala Phe Leu Ile Met Val Val Val Tyr Leu Arg Ile Tyr
200      205      210
Val Tyr Val Lys Arg Lys Thr Asn Val Leu Ser Pro His Thr Ser
215      220      225
Gly Ser Ile Ser Arg Arg Arg Thr Pro Met Lys Leu Met Lys Thr
230      235      240
Val Met Thr Val Leu Gly Ala Phe Val Val Cys Trp Thr Pro Gly
245      250      255
Leu Val Val Leu Leu Leu Asp Gly Leu Asn Cys Arg Gln Cys Gly
260      265      270
Val Gln His Val Lys Arg Trp Phe Leu Leu Leu Ala Leu Leu Asn
275      280      285
Ser Val Val Asn Pro Ile Ile Tyr Ser Tyr Lys Asp Glu Asp Met
290      295      300
Tyr Gly Thr Met Lys Lys Met Ile Cys Cys Phe Ser Gln Glu Asn
305      310      315
Pro Glu Arg Arg Pro Ser Arg Ile Pro Ser Thr Val Leu Ser Arg
320      325      330
Ser Asp Thr Gly Ser Gln Tyr Ile Glu Asp Ser Ile Ser Gln Gly
335      340      345
Ala Val Cys Asn Lys Ser Thr Ser
350

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&lt;210&gt; 20

&lt;211&gt; 361

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5029478CD1

&lt;400&gt; 20

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Met Ser Pro Glu Cys Ala Arg Ala Ala Gly Asp Ala Pro Leu Arg
1      5      10      15
Ser Leu Glu Gln Ala Asn Arg Thr Arg Phe Pro Phe Phe Ser Asp
20      25      30
Val Lys Gly Asp His Arg Leu Val Leu Ala Ala Val Glu Thr Thr
35      40      45
Val Leu Val Leu Ile Phe Ala Val Ser Leu Leu Gly Asn Val Cys

```

Ala	Leu	Val	Leu	Val	Ala	Arg	Arg	Arg	Arg	Arg	Gly	Ala	Thr	Ala	50	55	60
				65											70		75
Cys	Leu	Val	Leu	Asn	Leu	Phe	Cys	Ala	Asp	Leu	Leu	Phe	Ile	Ser	80	85	90
Ala	Ile	Pro	Leu	Val	Leu	Ala	Val	Arg	Trp	Thr	Glu	Ala	Trp	Leu	95	100	105
Leu	Gly	Pro	Val	Ala	Cys	His	Leu	Leu	Phe	Tyr	Val	Met	Thr	Leu	110	115	120
Ser	Gly	Ser	Val	Thr	Ile	Leu	Thr	Leu	Ala	Ala	Val	Ser	Leu	Glu	125	130	135
Arg	Met	Val	Cys	Ile	Val	His	Leu	Gln	Arg	Gly	Val	Arg	Gly	Pro	140	145	150
Gly	Arg	Arg	Ala	Arg	Ala	Val	Leu	Leu	Ala	Leu	Ile	Trp	Gly	Tyr	155	160	165
Ser	Ala	Val	Ala	Ala	Leu	Pro	Leu	Cys	Val	Phe	Phe	Arg	Val	Val	170	175	180
Pro	Gln	Arg	Leu	Pro	Gly	Ala	Asp	Gln	Glu	Ile	Ser	Ile	Cys	Thr	185	190	195
Leu	Ile	Trp	Pro	Thr	Ile	Pro	Gly	Glu	Ile	Ser	Trp	Asp	Val	Ser	200	205	210
Phe	Val	Thr	Leu	Asn	Phe	Leu	Val	Pro	Gly	Leu	Val	Ile	Val	Ile	215	220	225
Ser	Tyr	Ser	Lys	Ile	Leu	Gln	Ile	Thr	Lys	Ala	Ser	Arg	Lys	Arg	230	235	240
Leu	Thr	Val	Ser	Leu	Ala	Tyr	Ser	Glu	Ser	His	Gln	Ile	Arg	Val	245	250	255
Ser	Gln	Gln	Asp	Phe	Arg	Leu	Phe	Arg	Thr	Leu	Phe	Leu	Leu	Met	260	265	270
Val	Ser	Phe	Phe	Ile	Met	Trp	Ser	Pro	Ile	Ile	Ile	Thr	Ile	Leu	275	280	285
Leu	Ile	Leu	Ile	Gln	Asn	Phe	Lys	Gln	Asp	Leu	Val	Ile	Trp	Pro	290	295	300
Ser	Leu	Phe	Phe	Trp	Val	Val	Ala	Phe	Thr	Phe	Ala	Asn	Ser	Ala	305	310	315
Leu	Asn	Pro	Ile	Leu	Tyr	Asn	Met	Thr	Leu	Cys	Arg	Asn	Glu	Trp	320	325	330
Lys	Lys	Ile	Phe	Cys	Cys	Phe	Trp	Phe	Pro	Glu	Lys	Gly	Ala	Ile	335	340	345
Leu	Thr	Asp	Thr	Ser	Val	Lys	Arg	Asn	Asp	Leu	Ser	Ile	Ile	Ser	350	355	360

Gly

&lt;210&gt; 21

&lt;211&gt; 251

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5102576CD1

&lt;400&gt; 21

Met	Tyr	Leu	Val	Thr	Val	Leu	Arg	Asn	Leu	Phe	Ser	Ile	Leu	Ala	1	5	10	15
Val	Ser	Ser	Asp	Cys	Pro	Leu	His	Thr	Pro	Met	Tyr	Phe	Phe	Leu	20	25	30	35
Ser	Asn	Leu	Cys	Trp	Pro	Asp	Ile	Gly	Phe	Thr	Ser	Ala	Met	Val	40	45	50	55
Pro	Lys	Met	Ile	Val	Asp	Thr	Gln	Ser	His	Ser	Arg	Val	Ile	Ser	60	65	70	75
His	Ala	Gly	Cys	Leu	Thr	Gln	Met	Ser	Phe	Leu	Leu	Leu	Val	Ala	80	85	90	95
Cys	Ile	Glu	Gly	Met	Leu	Leu	Thr	Val	Met	Ala	Tyr	Asp	Cys	Phe	100	105	110	115
Val	Ala	Ile	Cys	Arg	Pro	Leu	His	Tyr	Pro	Val	Ile	Val	Asn	Pro	120	125	130	135

	95		100		105
His Leu Cys Val	Phe Phe Val Leu Val	Ser Phe Phe Leu Ser	Leu		
	110		115		120
Leu Asp Ser Gln	Leu His Ser Trp Ile	Val Leu Gln Leu Thr	Ile		
	125		130		135
Ile Lys Asn Val	Glu Ile Ser Asn Leu	Val Cys Asp Pro Ser	Gln		
	140		145		150
Leu Leu Asn Leu	Ala Cys Ser Asp Ser	Val Ile Asn Asn Ile	Phe		
	155		160		165
Ile Tyr Phe Asp	Ser Thr Met Phe Gly	Phe Leu Pro Ile Ser	Gly		
	170		175		180
Ile Phe Leu Ser	Tyr Tyr Lys Ile Val	Pro Ser Ile Leu Arg	Ile		
	185		190		195
Ser Ser Ser Asp	Gly Lys Tyr Lys Ala	Phe Ser Thr Cys Gly	Cys		
	200		205		210
His Leu Ala Val	Val Cys Trp Phe Tyr	Gly Thr Gly Ile Gly	Met		
	215		220		225
Tyr Leu Thr Ser	Ala Val Ser Pro Pro	Pro Arg Asn Gly Val	Val		
	230		235		240
Ala Ser Val Met	Tyr Ala Val Val Thr	Pro Cys			
	245		250		

&lt;210&gt; 22

&lt;211&gt; 315

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2200534CD1

&lt;400&gt; 22

Met Lys Ala Asn Tyr	Ser Ala Glu Glu Arg	Phe Leu Leu Leu Gly
1	5	10
Phe Ser Asp Trp Pro	Ser Leu Gln Pro Val	Leu Phe Ala Leu Val
	20	25
Leu Leu Cys Tyr Leu	Leu Thr Leu Thr Gly	Asn Ser Ala Leu Val
	35	40
Leu Leu Ala Val Arg	Asp Pro Arg Leu His	Thr Pro Met Tyr Tyr
	50	55
Phe Leu Cys His Leu	Ala Leu Val Asp Ala	Gly Phe Thr Thr Ser
	65	70
Val Val Pro Pro Leu	Leu Ala Asn Leu Arg	Gly Pro Ala Leu Trp
	80	85
Leu Pro Arg Ser His	Cys Thr Ala Gln Leu	Cys Ala Ser Leu Ala
	95	100
Leu Gly Ser Ala Glu	Cys Val Leu Leu Ala	Val Met Ala Leu Asp
	110	115
Arg Ala Ala Ala Val	Cys Arg Pro Leu Arg	Tyr Ala Gly Leu Val
	125	130
Ser Pro Arg Leu Cys	Arg Thr Leu Ala Ser	Ala Ser Trp Leu Ser
	140	145
Gly Leu Thr Asn Ser	Val Ala Gln Thr Ala	Leu Leu Ala Glu Arg
	155	160
Pro Leu Cys Ala Pro	Arg Leu Leu Asp His	Phe Ile Cys Glu Leu
	170	175
Pro Ala Leu Leu Lys	Leu Ala Cys Gly Gly	Asp Gly Asp Thr Thr
	185	190
Glu Asn Gln Met Phe	Ala Ala Arg Val Val	Ile Leu Leu Leu Pro
	200	205
Phe Ala Val Ile Leu	Ala Ser Tyr Gly Ala	Val Ala Arg Ala Val
	215	220
Cys Cys Met Arg Phe	Ser Gly Gly Arg Arg	Arg Ala Val Gly Thr
	230	235
Cys Gly Ser His Leu	Thr Ala Val Cys Leu	Phe Tyr Gly Ser Ala
	245	250
Ile Tyr Thr Tyr Leu	Gln Pro Ala Gln Arg	Tyr Asn Gln Ala Arg

	260		265		270
Gly Lys Phe Val	Ser Leu Phe Tyr Thr	Val Val Thr Pro Ala	Leu		
	275		280		285
Asn Pro Leu Ile	Tyr Thr Leu Arg Asn	Lys Lys Val Lys Gly	Ala		
	290		295		300
Ala Arg Arg Leu	Leu Arg Ser Leu Gly	Arg Gly Gln Ala Gly	Gln		
	305		310		315

&lt;210&gt; 23

&lt;211&gt; 470

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3275821CD1

&lt;400&gt; 23

Met Asp Thr Thr Met	Glu Ala Asp Leu	Gly Ala Thr Gly His	Arg
1	5	10	15
Pro Arg Thr Glu Leu	Asp Asp Glu Asp	Ser Tyr Pro Gln Gly	Gly
	20	25	30
Trp Asp Thr Val Phe	Leu Val Ala Leu	Leu Leu Gly Leu	Pro
	35	40	45
Ala Asn Gly Leu Met	Ala Trp Leu Ala	Gly Ser Gln Ala Arg	His
	50	55	60
Gly Ala Gly Thr Arg	Leu Ala Leu Leu	Leu Leu Ser Leu Ala	Leu
	65	70	75
Ser Asp Phe Leu Phe	Leu Ala Ala Ala	Ala Phe Gln Ile Leu	Glu
	80	85	90
Ile Arg His Gly Gly	His Trp Pro Leu	Gly Thr Ala Ala Cys	Arg
	95	100	105
Phe Tyr Tyr Phe Leu	Trp Gly Val Ser	Tyr Ser Ser Gly Leu	Phe
	110	115	120
Leu Leu Ala Ala Leu	Ser Leu Asp Arg	Cys Leu Leu Ala Leu	Cys
	125	130	135
Pro His Trp Tyr Pro	Gly His Arg Pro	Val Arg Leu Pro Leu	Trp
	140	145	150
Val Cys Ala Gly Val	Trp Val Leu Ala	Thr Leu Phe Ser Val	Pro
	155	160	165
Trp Leu Val Phe Pro	Glu Ala Ala Val	Trp Trp Tyr Asp Leu	Val
	170	175	180
Ile Cys Leu Asp Phe	Trp Asp Ser Glu	Glu Leu Ser Leu Arg	Met
	185	190	195
Leu Glu Val Leu Gly	Gly Phe Leu Pro	Phe Leu Leu Leu Leu	Val
	200	205	210
Cys His Val Leu Thr	Gln Ala Thr Ala	Cys Arg Thr Cys His	Arg
	215	220	225
Gln Gln Gln Pro Ala	Ala Cys Arg Gly	Phe Ala Arg Val Ala	Arg
	230	235	240
Thr Ile Leu Ser Ala	Tyr Val Val Leu	Arg Leu Pro Tyr Gln	Leu
	245	250	255
Ala Gln Leu Leu Tyr	Leu Ala Phe Leu	Trp Asp Val Tyr Ser	Gly
	260	265	270
Tyr Leu Leu Trp Glu	Ala Leu Val Tyr	Ser Asp Tyr Leu Ile	Leu
	275	280	285
Leu Asn Ser Cys Leu	Ser Pro Phe Leu	Cys Leu Met Ala Ser	Ala
	290	295	300
Asp Leu Arg Thr Leu	Leu Arg Ser Val	Leu Ser Ser Phe Ala	Ala
	305	310	315
Ala Leu Cys Glu Glu	Arg Pro Gly Ser	Phe Thr Pro Thr Glu	Pro
	320	325	330
Gln Thr Gln Leu Asp	Ser Glu Gly Pro	Thr Leu Pro Glu Pro	Met
	335	340	345
Ala Glu Ala Gln Ser	Gln Met Asp Pro	Val Ala Gln Pro Gln	Val
	350	355	360

Asn	Pro	Thr	Leu	Gln	Pro	Arg	Ser	Asp	Pro	Thr	Ala	Gln	Pro	Gln	
				365					370					375	
Leu	Asn	Pro	Thr	Ala	Gln	Pro	Gln	Ser	Asp	Pro	Thr	Ala	Gln	Pro	
				380					385					390	
Gln	Leu	Asn	Leu	Met	Ala	Gln	Pro	Gln	Ser	Asp	Ser	Val	Ala	Gln	
				395					400					405	
Pro	Gln	Ala	Asp	Thr	Asn	Val	Gln	Thr	Pro	Ala	Pro	Ala	Ala	Ser	
				410					415					420	
Ser	Val	Pro	Ser	Pro	Cys	Asp	Glu	Ala	Ser	Pro	Thr	Pro	Ser	Ser	
				425					430					435	
His	Pro	Thr	Pro	Gly	Ala	Leu	Glu	Asp	Pro	Ala	Thr	Pro	Pro	Ala	
				440					445					450	
Ser	Glu	Gly	Glu	Ser	Pro	Ser	Ser	Thr	Pro	Pro	Glu	Ala	Ala	Pro	
				455					460					465	
Gly	Ala	Gly	Pro	Thr											
				470											

&lt;210&gt; 24

&lt;211&gt; 358

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3744167CD1

&lt;400&gt; 24

Met	Ser	Val	Cys	Tyr	Arg	Pro	Pro	Gly	Asn	Glu	Thr	Leu	Leu	Ser	
1				5					10					15	
Trp	Lys	Thr	Ser	Arg	Ala	Thr	Gly	Thr	Ala	Phe	Leu	Leu	Leu	Ala	
				20					25					30	
Ala	Leu	Leu	Gly	Leu	Pro	Gly	Asn	Gly	Phe	Val	Val	Trp	Ser	Leu	
				35					40					45	
Ala	Gly	Trp	Arg	Pro	Ala	Arg	Gly	Arg	Pro	Leu	Ala	Ala	Thr	Leu	
				50					55					60	
Val	Leu	His	Leu	Ala	Leu	Ala	Asp	Gly	Ala	Val	Leu	Leu	Leu	Thr	
				65					70					75	
Pro	Leu	Phe	Val	Ala	Phe	Leu	Thr	Arg	Gln	Ala	Trp	Pro	Leu	Gly	
				80					85					90	
Gln	Ala	Gly	Cys	Lys	Ala	Val	Tyr	Tyr	Val	Cys	Ala	Leu	Ser	Met	
				95					100					105	
Tyr	Ala	Ser	Val	Leu	Leu	Thr	Gly	Leu	Leu	Ser	Leu	Gln	Arg	Cys	
				110					115					120	
Leu	Ala	Val	Thr	Arg	Pro	Phe	Leu	Ala	Pro	Arg	Leu	Arg	Ser	Pro	
				125					130					135	
Ala	Leu	Ala	Arg	Arg	Leu	Leu	Leu	Ala	Val	Trp	Leu	Ala	Ala	Leu	
				140					145					150	
Leu	Leu	Ala	Val	Pro	Ala	Ala	Val	Tyr	Arg	His	Leu	Trp	Arg	Asp	
				155					160					165	
Arg	Val	Cys	Gln	Leu	Cys	His	Pro	Ser	Pro	Val	His	Ala	Ala	Ala	
				170					175					180	
His	Leu	Ser	Leu	Glu	Thr	Leu	Thr	Ala	Phe	Val	Leu	Pro	Phe	Gly	
				185					190					195	
Leu	Met	Leu	Gly	Cys	Tyr	Ser	Val	Thr	Leu	Ala	Arg	Leu	Arg	Gly	
				200					205					210	
Ala	Arg	Trp	Gly	Ser	Gly	Arg	His	Gly	Ala	Arg	Val	Gly	Arg	Leu	
				215					220					225	
Val	Ser	Ala	Ile	Val	Leu	Ala	Phe	Gly	Leu	Leu	Trp	Ala	Pro	Tyr	
				230					235					240	
His	Ala	Val	Asn	Leu	Leu	Gln	Ala	Val	Ala	Ala	Leu	Ala	Pro	Pro	
				245					250					255	
Glu	Gly	Ala	Leu	Ala	Lys	Leu	Gly	Gly	Ala	Gly	Gln	Ala	Ala	Arg	
				260					265					270	
Ala	Gly	Thr	Thr	Ala	Leu	Ala	Phe	Phe	Ser	Ser	Ser	Val	Asn	Pro	
				275					280					285	
Val	Leu	Tyr	Val	Phe	Thr	Ala	Gly	Asp	Leu	Leu	Pro	Arg	Ala	Gly	
				290					295					300	

Pro	Arg	Phe	Leu	Thr	Arg	Leu	Phe	Glu	Gly	Ser	Gly	Glu	Ala	Arg
				305					310					315
Gly	Gly	Gly	Arg	Ser	Arg	Glu	Gly	Thr	Met	Glu	Leu	Arg	Thr	Thr
				320					325					330
Pro	Gln	Leu	Lys	Val	Val	Gly	Gln	Gly	Arg	Gly	Asn	Gly	Asp	Pro
				335					340					345
Gly	Gly	Gly	Met	Glu	Lys	Asp	Gly	Pro	Glu	Trp	Asp	Leu		
				350					355					

&lt;210&gt; 25

&lt;211&gt; 314

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472007CD1

&lt;400&gt; 25

Met	Trp	Glu	Asn	Trp	Thr	Ile	Val	Ser	Glu	Phe	Val	Leu	Val	Ser
1				5					10					15
Phe	Ser	Ala	Leu	Ser	Thr	Glu	Leu	Gln	Ala	Leu	Leu	Phe	Leu	Leu
				20					25					30
Phe	Leu	Thr	Ile	Tyr	Leu	Val	Thr	Leu	Met	Gly	Asn	Val	Leu	Ile
				35					40					45
Ile	Leu	Val	Thr	Ile	Ala	Asp	Ser	Ala	Leu	Gln	Ser	Pro	Met	Tyr
				50					55					60
Phe	Phe	Leu	Arg	Asn	Leu	Ser	Phe	Leu	Glu	Ile	Gly	Phe	Asn	Leu
				65					70					75
Val	Ile	Val	Pro	Lys	Met	Leu	Gly	Thr	Leu	Ile	Ile	Gln	Asp	Thr
				80					85					90
Thr	Ile	Ser	Phe	Leu	Gly	Cys	Ala	Thr	Gln	Met	Tyr	Phe	Phe	Phe
				95					100					105
Phe	Phe	Gly	Ala	Ala	Glu	Cys	Cys	Leu	Leu	Ala	Thr	Met	Ala	Tyr
				110					115					120
Asp	Arg	Tyr	Val	Ala	Ile	Cys	Asp	Pro	Leu	His	Tyr	Pro	Val	Ile
				125					130					135
Met	Gly	His	Ile	Ser	Cys	Ala	Gln	Leu	Ala	Ala	Ala	Ser	Trp	Phe
				140					145					150
Ser	Gly	Phe	Ser	Val	Ala	Thr	Val	Gln	Thr	Thr	Trp	Ile	Phe	Ser
				155					160					165
Phe	Pro	Phe	Cys	Gly	Pro	Asn	Arg	Val	Asn	His	Phe	Phe	Cys	Asp
				170					175					180
Ser	Pro	Pro	Val	Ile	Ala	Leu	Val	Cys	Ala	Asp	Thr	Ser	Val	Phe
				185					190					195
Glu	Leu	Glu	Ala	Leu	Thr	Ala	Thr	Val	Pro	Phe	Ile	Leu	Phe	Pro
				200					205					210
Phe	Leu	Leu	Ile	Leu	Gly	Ser	Tyr	Val	Arg	Ile	Leu	Ser	Thr	Ile
				215					220					225
Phe	Arg	Met	Pro	Ser	Ala	Glu	Gly	Lys	His	Gln	Ala	Phe	Ser	Thr
				230					235					240
Cys	Ser	Ala	His	Leu	Leu	Val	Val	Ser	Leu	Phe	Tyr	Ser	Thr	Ala
				245					250					255
Ile	Leu	Thr	Tyr	Phe	Arg	Pro	Gln	Ser	Ser	Ala	Ser	Ser	Glu	Ser
				260					265					270
Lys	Lys	Leu	Leu	Ser	Leu	Ser	Ser	Thr	Val	Val	Thr	Pro	Met	Leu
				275					280					285
Asn	Pro	Ile	Ile	Tyr	Ser	Ser	Arg	Asn	Lys	Glu	Val	Lys	Ala	Ala
				290					295					300
Leu	Lys	Arg	Leu	Ile	His	Arg	Thr	Leu	Gly	Ser	Gln	Lys	Leu	
				305					310					

&lt;210&gt; 26

&lt;211&gt; 365

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472008CD1

&lt;400&gt; 26

Met	Glu	Gly	Ser	Val	Glu	Ala	Thr	Pro	Glu	Ile	Pro	Ala	Gln	Met	1	5	10	15
Lys	Cys	His	Pro	Ser	Arg	Pro	Ser	Thr	Leu	Asn	Gln	Leu	Ser	Phe	20	25	30	35
Tyr	Gly	Ala	Val	Ser	Ser	Leu	Gly	Arg	Met	His	Gly	Leu	Glu	Thr	40	45	50	55
Lys	Ser	Ser	Ala	Glu	Ile	Arg	Ala	Gly	Leu	Lys	Arg	Cys	Asp	Thr	60	65	70	75
Leu	Val	Leu	Glu	Ala	Ser	Thr	Leu	Glu	Gly	Asn	Met	Val	Ile	Val	80	85	90	95
Leu	Val	Ser	Leu	Lys	Asp	Pro	Lys	Leu	His	Ile	Pro	Met	Tyr	Phe	100	105	110	115
Phe	Leu	Ser	Asn	Leu	Ser	Leu	Val	Asp	Leu	Cys	Leu	Thr	Ser	Ser	120	125	130	135
Cys	Val	Pro	Gln	Met	Leu	Ile	Asn	Phe	Trp	Gly	Pro	Glu	Lys	Thr	140	145	150	155
Ile	Ser	Tyr	Ile	Gly	Cys	Ala	Ile	Gln	Leu	Tyr	Val	Phe	Leu	Trp	160	165	170	175
Leu	Gly	Ala	Thr	Glu	Tyr	Val	Leu	Leu	Val	Val	Met	Ala	Val	Asp	180	185	190	195
Cys	Tyr	Val	Ala	Val	Cys	His	Pro	Leu	Gln	Asn	Thr	Met	Ile	Met	200	205	210	215
His	Pro	Lys	Leu	Cys	Leu	Gln	Leu	Ala	Ile	Leu	Ala	Trp	Gly	Thr	220	225	230	235
Gly	Leu	Ala	Gln	Ser	Leu	Ile	Gln	Ser	Pro	Ala	Thr	Leu	Arg	Leu	240	245	250	255
Pro	Phe	Cys	Ser	Gln	Arg	Met	Val	Asp	Asp	Val	Val	Cys	Glu	Val	260	265	270	275
Pro	Ala	Leu	Ile	Gln	Leu	Ser	Ser	Thr	Asp	Thr	Thr	Tyr	Ser	Glu	280	285	290	295
Ile	Gln	Met	Ser	Ile	Ala	Ser	Val	Val	Leu	Leu	Val	Met	Pro	Leu	300	305	310	315
Ile	Ile	Ile	Leu	Ser	Ser	Ser	Gly	Ala	Ile	Ala	Lys	Ala	Val	Leu	320	325	330	335
Arg	Ile	Lys	Ser	Thr	Ala	Gly	Gln	Lys	Lys	Ala	Phe	Gly	Thr	Cys	340	345	350	355
Ile	Ser	His	Leu	Leu	Val	Val	Ser	Leu	Phe	Tyr	Gly	Thr	Val	Thr	360			
Gly	Val	Tyr	Leu	Gln	Pro	Lys	Asn	His	Tyr	Pro	His	Glu	Trp	Gly				
Lys	Phe	Leu	Thr	Leu	Phe	Tyr	Thr	Val	Val	Thr	Pro	Thr	Leu	Asn				
Pro	Leu	Ile	Tyr	Thr	Leu	Arg	Asn	Lys	Glu	Leu	His	Pro	Trp	Leu				
Lys	Glu	Ala	Lys	Val	Gln	Thr	Ala	Ser	Glu	Ser	Ala	Ser	Pro	Lys				
His	Trp	Gln	Leu	Pro	His	Gly	Val	Gly	Pro	Val	Gly	Val	Gln	Lys				
Thr	Arg	Thr	Glu	Leu														

&lt;210&gt; 27

&lt;211&gt; 317

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472013CD1

&lt;400&gt; 27

Met	Ser	Phe	Ala	Pro	Asn	Ala	Ser	His	Ser	Pro	Val	Phe	Leu	Leu
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----



1	5	10	15
Leu Gly Phe Ser Arg	Ala Asn Ile Ser Tyr Thr Leu Leu Phe Phe		
20	25	30	
Leu Phe Leu Ala Ile Tyr Leu Thr Thr Ile Leu Gly Asn Val Thr			
35	40	45	
Leu Val Leu Leu Ile Ser Trp Asp Ser Arg Leu His Ser Pro Met			
50	55	60	
Tyr Tyr Leu Leu Arg Gly Leu Ser Val Ile Asp Met Gly Leu Ser			
65	70	75	
Thr Val Thr Leu Pro Gln Leu Leu Ala His Leu Val Ser His Tyr			
80	85	90	
Pro Thr Ile Pro Ala Ala Arg Cys Leu Ala Gln Phe Phe Phe Phe			
95	100	105	
Tyr Ala Phe Gly Val Thr Asp Thr Leu Val Ile Ala Val Met Ala			
110	115	120	
Leu Asp Arg Tyr Val Ala Ile Cys Asp Pro Leu His Tyr Ala Leu			
125	130	135	
Val Met Asn His Gln Arg Cys Ala Cys Leu Leu Ala Leu Ser Trp			
140	145	150	
Val Val Ser Ile Leu His Thr Met Leu Arg Val Gly Leu Val Leu			
155	160	165	
Pro Leu Cys Trp Thr Gly Asp Ala Gly Gly Asn Val Asn Leu Pro			
170	175	180	
His Phe Phe Cys Asp His Arg Pro Leu Leu Arg Ala Ser Cys Ser			
185	190	195	
Asp Ile His Ser Asn Glu Leu Ala Ile Phe Phe Glu Gly Gly Phe			
200	205	210	
Leu Met Leu Gly Pro Cys Ala Leu Ile Val Leu Ser Tyr Val Arg			
215	220	225	
Ile Gly Ala Ala Ile Leu Arg Leu Pro Ser Ala Ala Gly Arg Arg			
230	235	240	
Arg Ala Val Ser Thr Cys Gly Ser His Leu Thr Met Val Gly Phe			
245	250	255	
Leu Tyr Gly Thr Ile Ile Cys Val Tyr Phe Gln Pro Pro Phe Gln			
260	265	270	
Asn Ser Gln Tyr Gln Asp Met Val Ala Ser Val Met Tyr Thr Ala			
275	280	285	
Ile Thr Pro Leu Ala Asn Pro Phe Val Tyr Ser Leu His Asn Lys			
290	295	300	
Asp Val Lys Gly Ala Leu Cys Arg Leu Leu Glu Trp Val Lys Val			
305	310	315	

Asp Pro

&lt;210&gt; 28

&lt;211&gt; 335

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472015CD1

&lt;400&gt; 28

Met Glu Ser Ser Phe	Ser Phe Gly Val Ile Leu Ala Val Leu Ala
1	5
Ser Leu Ile Ile Ala	Thr Asn Thr Leu Val Ala Val Ala Val Leu
20	25
Leu Leu Ile His Lys	Asn Asp Gly Val Ser Leu Cys Phe Thr Leu
35	40
Asn Leu Ala Val Ala	Asp Thr Leu Ile Gly Val Ala Ile Ser Gly
50	55
Leu Leu Thr Asp Gln	Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys
65	70
Thr Leu Cys Ser Leu	Arg Met Ala Phe Val Thr Ser Ser Ala Ala
80	85
Ala Ser Val Leu Thr	Val Met Leu Ile Thr Phe Asp Arg Tyr Leu

	95		100		105									
Ala	Ile	Lys	Gln	Pro	Phe	Arg	Tyr	Leu	Lys	Ile	Met	Ser	Gly	Phe
	110								115					120
Val	Ala	Gly	Ala	Cys	Ile	Ala	Gly	Leu	Trp	Leu	Val	Ser	Tyr	Leu
	125								130					135
Ile	Gly	Phe	Leu	Pro	Leu	Gly	Ile	Pro	Met	Phe	Gln	Gln	Thr	Ala
	140								145					150
Tyr	Lys	Gly	Gln	Cys	Ser	Phe	Phe	Ala	Val	Phe	His	Pro	His	Phe
	155								160					165
Val	Leu	Thr	Leu	Ser	Cys	Val	Gly	Phe	Phe	Pro	Ala	Met	Leu	Leu
	170								175					180
Phe	Val	Phe	Phe	Tyr	Cys	Asp	Met	Leu	Lys	Ile	Ala	Ser	Met	His
	185								190					195
Ser	Gln	Gln	Ile	Arg	Lys	Met	Glu	His	Ala	Gly	Ala	Met	Ala	Gly
	200								205					210
Gly	Tyr	Arg	Ser	Pro	Arg	Thr	Pro	Ser	Asp	Phe	Lys	Ala	Leu	Arg
	215								220					225
Thr	Val	Ser	Val	Leu	Ile	Gly	Ser	Phe	Ala	Leu	Ser	Trp	Thr	Pro
	230								235					240
Phe	Leu	Ile	Thr	Gly	Ile	Val	Gln	Val	Ala	Cys	Gln	Glu	Cys	His
	245								250					255
Leu	Tyr	Leu	Val	Leu	Glu	Arg	Tyr	Leu	Trp	Leu	Leu	Gly	Val	Gly
	260								265					270
Asn	Ser	Leu	Leu	Asn	Pro	Leu	Ile	Tyr	Ala	Tyr	Trp	Gln	Lys	Glu
	275								280					285
Val	Arg	Leu	Gln	Leu	Tyr	His	Met	Ala	Leu	Gly	Val	Lys	Lys	Val
	290								295					300
Leu	Thr	Ser	Phe	Leu	Leu	Phe	Leu	Ser	Ala	Arg	Asn	Cys	Gly	Pro
	305								310					315
Glu	Arg	Pro	Arg	Glu	Ser	Ser	Cys	His	Ile	Val	Thr	Ile	Ser	Ser
	320								325					330
Ser	Glu	Phe	Asp	Gly										
	335													

<210> 29  
 <211> 309  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7472016CD1

<400>	29													
Met	Arg	Glu	Asn	Asn	Gln	Ser	Ser	Thr	Leu	Glu	Phe	Ile	Leu	Leu
1			5						10					15
Gly	Val	Thr	Gly	Gln	Gln	Glu	Gln	Glu	Asp	Phe	Phe	Tyr	Ile	Leu
			20						25					30
Phe	Leu	Phe	Ile	Tyr	Pro	Ile	Thr	Leu	Ile	Gly	Asn	Leu	Leu	Ile
			35						40					45
Val	Leu	Ala	Ile	Cys	Ser	Asp	Val	Arg	Leu	His	Asn	Pro	Met	Tyr
			50						55					60
Phe	Leu	Leu	Ala	Asn	Leu	Ser	Leu	Val	Asp	Ile	Phe	Phe	Ser	Ser
			65						70					75
Val	Thr	Ile	Pro	Lys	Met	Leu	Ala	Asn	His	Leu	Leu	Gly	Ser	Lys
			80						85					90
Ser	Ile	Ser	Phe	Gly	Gly	Cys	Leu	Thr	Gln	Met	Tyr	Phe	Met	Ile
			95						100					105
Ala	Leu	Gly	Asn	Thr	Asp	Ser	Tyr	Ile	Leu	Ala	Ala	Met	Ala	Tyr
			110						115					120
Asp	Arg	Ala	Val	Ala	Ile	Ser	His	Pro	Leu	His	Tyr	Thr	Thr	Ile
			125						130					135
Met	Ser	Pro	Arg	Ser	Cys	Ile	Trp	Leu	Ile	Ala	Gly	Ser	Trp	Val
			140						145					150
Ile	Gly	Asn	Ala	Asn	Ala	Leu	Pro	His	Thr	Leu	Leu	Thr	Ala	Ser
			155						160					165
Leu	Ser	Phe	Cys	Gly	Asn	Gln	Glu	Val	Ala	Asn	Phe	Tyr	Cys	Asp

Ile Thr Pro Leu	170	Lys Leu Ser Cys	175	Ser Asp Ile His Phe	180
Val Lys Met Met	185	Leu Gly Val Gly	190	Ile Phe Ser Val Pro	195
Leu Cys Ile Ile	200	Ser Tyr Ile Arg	205	Val Phe Ser Thr Val	210
Gln Val Pro Ser	215	Lys Gly Val Leu	220	Lys Ala Phe Ser Thr	225
Gly Ser His Leu	230	Val Val Ser Leu	235	Tyr Gly Thr Val	240
Gly Thr Tyr Phe	245	Pro Leu Thr Asn	250	Ser Leu Lys Asp	255
Val Ile Thr Val	260	Tyr Thr Ala Val	265	Thr Pro Met Leu Asn	270
Phe Ile Tyr Ser	275	Leu Arg Asn Arg	280	Met Lys Ala Ala Leu	285
Lys Leu Phe Asn	290	Lys Arg Ile Ser	295		300
	305				

<210> 30  
 <211> 236  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7472017CD1

Met Gly Met Thr	Asn	Ser Ser Val Lys	Gly	Asp Phe Ile Leu	Leu
1	5		10		15
Leu Trp Asn Leu	Lys	Gly Pro Asp Lys	Thr	Ile Thr Phe Leu	Gly
	20		25		30
Cys Val Ile Gln	Leu	Tyr Ile Ser Leu	Ala	Leu Gly Ser Thr	Glu
	35		40		45
Cys Val Leu Leu	Ala	Val Met Ala Phe	Asp	Arg Tyr Ala Ala	Val
	50		55		60
Cys Lys Pro Leu	His	Tyr Thr Ala Val	Met	Asn Pro Gln Leu	Cys
	65		70		75
Gln Ala Leu Ala	Gly	Val Ala Trp Leu	Ser	Gly Val Gly Asn	Thr
	80		85		90
Leu Ile Gln Gly	Thr	Val Thr Leu Trp	Leu	Pro Arg Cys Gly	His
	95		100		105
Arg Leu Leu Gln	His	Phe Phe Leu Ala	Cys	Val Asp Ile His	Asp
	110		115		120
Asn Glu Val Gln	Leu	Phe Val Ala Ser	Leu	Val Leu Leu Leu	Leu
	125		130		135
Pro Leu Val Leu	Ile	Leu Leu Ser Tyr	Gly	His Ile Ala Lys	Val
	140		145		150
Val Ile Arg Ile	Lys	Ser Val Gln Ala	Trp	Cys Lys Gly Leu	Gly
	155		160		165
Thr Cys Gly Ser	His	Leu Ile Val Val	Ser	Leu Phe Cys Gly	Thr
	170		175		180
Ile Thr Ala Val	Tyr	Ile Gln Ser Asn	Ser	Ser Tyr Ala His	Ala
	185		190		195
His Gly Lys Phe	Ile	Ser Leu Phe Tyr	Thr	Val Val Thr Pro	Thr
	200		205		210
Leu Asn Pro Leu	Ile	Tyr Thr Leu Arg	Asn	Asn Asp Val Lys	Gly
	215		220		225
Ala Leu Arg Leu	Phe	Asn Arg Asp Leu	Gly	Thr	
	230		235		

<210> 31  
 <211> 363  
 <212> PRT  
 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472018CD1

&lt;400&gt; 31

Met	Gly	Pro	Gly	Glu	Ala	Leu	Leu	Ala	Gly	Leu	Leu	Val	Met	Val
1				5					10					15
Leu	Ala	Val	Ala	Leu	Leu	Ser	Asn	Ala	Leu	Val	Leu	Leu	Cys	Cys
				20					25					30
Ala	Tyr	Ser	Ala	Glu	Leu	Arg	Thr	Arg	Ala	Ser	Gly	Val	Leu	Leu
				35					40					45
Val	Asn	Leu	Ser	Leu	Gly	His	Leu	Leu	Leu	Ala	Ala	Leu	Asp	Met
				50					55					60
Pro	Phe	Thr	Leu	Leu	Gly	Val	Met	Arg	Gly	Arg	Thr	Pro	Ser	Ala
				65					70					75
Pro	Gly	Ala	Cys	Gln	Val	Ile	Gly	Phe	Leu	Asp	Thr	Phe	Leu	Ala
				80					85					90
Ser	Asn	Ala	Ala	Leu	Ser	Val	Ala	Ala	Leu	Ser	Ala	Asp	Gln	Trp
				95					100					105
Leu	Ala	Val	Gly	Phe	Pro	Leu	Arg	Tyr	Ala	Gly	Arg	Leu	Arg	Pro
				110					115					120
Arg	Tyr	Ala	Gly	Leu	Leu	Leu	Gly	Cys	Ala	Trp	Gly	Gln	Ser	Leu
				125					130					135
Ala	Phe	Ser	Gly	Ala	Ala	Leu	Gly	Cys	Ser	Trp	Leu	Gly	Tyr	Ser
				140					145					150
Ser	Ala	Phe	Ala	Ser	Cys	Ser	Leu	Arg	Leu	Pro	Pro	Glu	Pro	Glu
				155					160					165
Arg	Pro	Arg	Phe	Ala	Ala	Phe	Thr	Ala	Thr	Leu	His	Ala	Val	Gly
				170					175					180
Phe	Val	Leu	Pro	Leu	Ala	Val	Leu	Cys	Leu	Thr	Ser	Leu	Gln	Val
				185					190					195
His	Arg	Val	Ala	Arg	Arg	His	Cys	Gln	Arg	Met	Asp	Thr	Val	Thr
				200					205					210
Met	Lys	Ala	Leu	Ala	Leu	Leu	Ala	Asp	Leu	His	Pro	Ser	Val	Arg
				215					220					225
Gln	Arg	Cys	Leu	Ile	Gln	Gln	Lys	Arg	Arg	Arg	His	Arg	Ala	Thr
				230					235					240
Arg	Lys	Ile	Gly	Ile	Ala	Ile	Ala	Thr	Phe	Leu	Ile	Cys	Phe	Ala
				245					250					255
Pro	Tyr	Val	Met	Thr	Arg	Leu	Ala	Glu	Leu	Val	Pro	Phe	Val	Thr
				260					265					270
Val	Asn	Ala	Gln	Trp	Gly	Ile	Leu	Ser	Lys	Cys	Leu	Thr	Tyr	Ser
				275					280					285
Lys	Ala	Val	Ala	Asp	Pro	Phe	Thr	Tyr	Ser	Leu	Leu	Arg	Arg	Pro
				290					295					300
Phe	Arg	Gln	Val	Leu	Ala	Gly	Met	Val	His	Arg	Leu	Leu	Lys	Arg
				305					310					315
Thr	Pro	Arg	Pro	Ala	Ser	Thr	His	Asp	Ser	Ser	Leu	Asp	Val	Ala
				320					325					330
Gly	Met	Val	His	Gln	Leu	Leu	Lys	Arg	Thr	Pro	Arg	Pro	Ala	Ser
				335					340					345
Thr	His	Asn	Gly	Ser	Val	Asp	Thr	Glu	Asn	Asp	Ser	Cys	Leu	Gln
				350					355					360

Gln Thr His

&lt;210&gt; 32

&lt;211&gt; 308

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472019CD1

&lt;400&gt; 32

Met Ala Met Asp Asn Val Thr Ala Val Phe Gln Phe Leu Leu Ile

1	5	10	15
Gly Ile Ser Asn Tyr	Pro Gln Trp Arg Asp	Thr Phe Phe Thr	Leu
20	25	30	
Val Leu Ile Ile Tyr	Leu Ser Thr Leu Leu Gly	Asn Gly Phe	Met
35	40	45	
Ile Phe Leu Ile His	Phe Asp Pro Asn Leu	His Thr Pro Ile	Tyr
50	55	60	
Phe Phe Leu Ser Asn	Leu Ser Phe Leu Asp	Leu Cys Tyr Gly	Thr
65	70	75	
Ala Ser Met Pro Gln	Ala Leu Val His Cys	Phe Ser Thr His	Pro
80	85	90	
Tyr Leu Ser Tyr Pro	Arg Cys Leu Ala Gln	Thr Ser Val Ser	Leu
95	100	105	
Ala Leu Ala Thr Ala	Glu Cys Leu Leu Leu	Ala Ala Met Ala	Tyr
110	115	120	
Asp Arg Val Val Ala	Ile Ser Asn Pro Leu	Arg Tyr Ser Val	Val
125	130	135	
Met Asn Gly Pro Val	Cys Val Cys Leu Val	Ala Thr Ser Trp	Gly
140	145	150	
Thr Ser Leu Val Leu	Thr Ala Met Leu Ile	Leu Ser Leu Arg	Leu
155	160	165	
His Phe Cys Gly Ala	Asn Val Ile Asn His	Phe Ala Cys Glu	Ile
170	175	180	
Leu Ser Leu Ile Lys	Leu Thr Cys Ser Asp	Thr Ser Leu Asn	Glu
185	190	195	
Phe Met Ile Leu Ile	Thr Ser Ile Phe Thr	Leu Leu Leu Pro	Phe
200	205	210	
Gly Phe Val Leu Leu	Ser Tyr Ile Arg Ile	Ala Met Ala Ile	Ile
215	220	225	
Arg Ile Arg Ser Leu	Gln Gly Arg Leu Lys	Ala Phe Thr Thr	Cys
230	235	240	
Gly Ser His Leu Thr	Val Val Thr Ile Phe	Tyr Gly Ser Ala	Ile
245	250	255	
Ser Met Tyr Met Lys	Thr Gln Ser Lys Ser	Tyr Pro Asp Gln	Asp
260	265	270	
Lys Phe Ile Ser Val	Phe Tyr Gly Ala Leu	Thr Pro Met Leu	Asn
275	280	285	
Pro Leu Ile Tyr Ser	Leu Arg Lys Lys Asp	Val Lys Arg Ala	Ile
290	295	300	
Arg Lys Val Met Leu	Lys Arg Thr		
305			

<210> 33  
 <211> 343  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7472021CD1

<400> 33
Met His Phe Leu Pro Thr Val Phe Gly Phe Leu Asn Arg Val Thr
1 5 10 15
Leu Gly Ile Phe Arg Glu Thr Met Val Asn Leu Thr Ser Met Ser
20 25 30
Gly Phe Leu Leu Met Gly Phe Ser Asp Glu Arg Lys Leu Gln Ile
35 40 45
Leu His Ala Leu Val Phe Leu Val Thr Tyr Leu Leu Ala Leu Thr
50 55 60
Gly Asn Leu Leu Ile Ile Thr Ile Ile Thr Val Asp Arg Arg Leu
65 70 75
His Ser Pro Met Tyr Tyr Phe Leu Lys His Leu Ser Leu Leu Asp
80 85 90
Leu Cys Phe Ile Ser Val Thr Val Pro Gln Ser Ile Ala Asn Ser
95 100 105
Leu Met Gly Asn Gly Tyr Ile Ser Leu Val Gln Cys Ile Leu Gln

Val	Phe	Phe	Phe	Ile	Ala	Leu	Ala	Ser	Ser	Glu	Val	Ala	Ile	Leu	110	115	120
				125											125	130	135
Thr	Val	Met	Ser	Tyr	Asp	Arg	Tyr	Ala	Ala	Ile	Cys	Gln	Pro	Leu	140	145	150
His	Tyr	Glu	Thr	Ile	Met	Asp	Pro	Arg	Ala	Cys	Arg	His	Ala	Val	155	160	165
Ile	Ala	Val	Trp	Ile	Ala	Gly	Gly	Leu	Ser	Gly	Leu	Met	His	Ala	170	175	180
Ala	Ile	Asn	Phe	Ser	Ile	Pro	Leu	Cys	Gly	Lys	Arg	Val	Ile	His	185	190	195
Gln	Phe	Phe	Cys	Asp	Val	Pro	Gln	Met	Leu	Lys	Leu	Ala	Cys	Ser	200	205	210
Tyr	Glu	Phe	Ile	Asn	Glu	Ile	Ala	Leu	Ala	Ala	Phe	Thr	Thr	Ser	215	220	225
Ala	Ala	Phe	Ile	Cys	Leu	Ile	Ser	Ile	Val	Leu	Ser	Tyr	Ile	Arg	230	235	240
Ile	Phe	Ser	Thr	Val	Leu	Arg	Ile	Pro	Ser	Ala	Glu	Gly	Arg	Thr	245	250	255
Lys	Val	Phe	Ser	Thr	Cys	Leu	Pro	His	Leu	Phe	Val	Ala	Thr	Phe	260	265	270
Phe	Leu	Ser	Ala	Ala	Gly	Phe	Glu	Phe	Leu	Arg	Leu	Pro	Ser	Asp	275	280	285
Ser	Ser	Ser	Thr	Val	Asp	Leu	Val	Phe	Ser	Val	Phe	Tyr	Thr	Val	290	295	300
Ile	Pro	Pro	Thr	Leu	Asn	Pro	Val	Ile	Tyr	Ser	Leu	Arg	Asn	Asp	305	310	315
Ser	Met	Lys	Ala	Ala	Leu	Arg	Lys	Met	Leu	Ser	Lys	Glu	Glu	Leu	320	325	330
Pro	Gln	Arg	Lys	Met	Cys	Leu	Lys	Ala	Met	Phe	Lys	Leu			335	340	

&lt;210&gt; 34

&lt;211&gt; 323

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472009CD1

&lt;400&gt; 34

Met	Trp	Gln	Lys	Asn	Gln	Thr	Ser	Leu	Ala	Asp	Phe	Ile	Leu	Glu	1	5	10	15
Gly	Leu	Phe	Asp	Asp	Ser	Leu	Thr	His	Leu	Phe	Leu	Phe	Ser	Leu	20	25	30	35
Thr	Met	Val	Val	Phe	Leu	Ile	Ala	Val	Ser	Gly	Asn	Thr	Leu	Thr	35	40	45	50
Ile	Leu	Leu	Ile	Cys	Ile	Asp	Pro	Gln	Leu	His	Thr	Pro	Met	Tyr	50	55	60	65
Phe	Leu	Leu	Ser	Gln	Leu	Ser	Leu	Met	Asp	Leu	Met	His	Val	Ser	65	70	75	80
Thr	Thr	Ile	Leu	Lys	Met	Ala	Thr	Asn	Tyr	Leu	Ser	Gly	Lys	Lys	80	85	90	95
Ser	Ile	Ser	Phe	Val	Gly	Cys	Ala	Thr	Gln	His	Phe	Leu	Tyr	Leu	95	100	105	110
Cys	Leu	Gly	Gly	Ala	Glu	Cys	Phe	Leu	Leu	Ala	Val	Met	Ser	Tyr	110	115	120	125
Asp	Arg	Tyr	Val	Ala	Ile	Cys	His	Pro	Leu	Arg	Tyr	Ala	Val	Leu	125	130	135	140
Met	Asn	Lys	Lys	Val	Gly	Leu	Met	Met	Ala	Val	Met	Ser	Trp	Leu	140	145	150	155
Gly	Ala	Ser	Val	Asn	Ser	Leu	Ile	His	Met	Ala	Ile	Leu	Met	His	155	160	165	170
Phe	Pro	Phe	Cys	Gly	Pro	Arg	Lys	Val	Tyr	His	Phe	Tyr	Cys	Glu	170	175	180	
Phe	Pro	Ala	Val	Val	Lys	Leu	Val	Cys	Gly	Asp	Ile	Thr	Val	Tyr				

Glu Thr Thr Val	185	Ile Ser Ser Ile	190	Leu Leu Leu Pro	195
Phe Leu Ile Ser	200	Thr Ser Tyr Val Phe	205	Ile Leu Gln Ser Val	210
Gln Met Arg Ser	215	Gly Ser Lys Arg	220	Asn Ala Phe Ala Thr	225
Gly Ser His Leu	230	Thr Val Val Ser Leu	235	Trp Phe Gly Ala Cys	240
Phe Ser Tyr Met	245	Arg Pro Arg Ser Gln	250	Cys Thr Leu Leu Gln	255
Lys Val Gly Ser	260	Val Phe Tyr Ser Ile	265	Ile Thr Pro Thr Leu	270
Ser Leu Ile Tyr	275	Thr Leu Arg Asn Lys	280	Asp Val Ala Lys Ala	285
Arg Arg Val Leu	290	Arg Asp Val Ile	295	Thr Gln Cys Ile Gln	300
Leu Gln Leu Trp	305	Leu Pro Arg Val	310		315
	320				

&lt;210&gt; 35

&lt;211&gt; 299

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472010CD1

&lt;400&gt; 35

Met Glu Leu Glu Gly	1	Asp Phe Leu Gly	10	Ser Val Gly Glu Leu Gly	15
Gln Val Ile Gln Thr	20	Cys Ser Gly Ile Tyr	25	Val Phe Thr Val Val	30
Gly Asn Leu Gly Leu	35	Ile Thr Leu Ile Gly	40	Ile Asn Pro Ser Leu	45
His Thr Pro Met Tyr	50	Phe Phe Leu Phe Asn	55	Leu Ser Phe Ile Asp	60
Leu Cys Tyr Ser Cys	65	Val Phe Thr Pro Lys	70	Met Leu Asn Asp Phe	75
Val Ser Glu Ser Ile	80	Ile Ser Tyr Val Gly	85	Cys Met Thr Gln Leu	90
Phe Phe Phe Cys Phe	95	Phe Val Asn Ser Glu	100	Cys Tyr Val Leu Val	105
Ser Met Ala Tyr Asp	110	Arg Tyr Val Ala Ile	115	Cys Asn Pro Leu Leu	120
Tyr Met Val Thr Met	125	Ser Pro Arg Val Cys	130	Phe Leu Leu Met Phe	135
Gly Ser Tyr Val Val	140	Gly Phe Ala Gly Ala	145	Met Ala His Thr Gly	150
Ser Met Leu Arg Leu	155	Thr Phe Cys Asp Ser	160	Asn Val Ile Asp His	165
Tyr Leu Cys Asp Val	170	Leu Pro Leu Leu Gln	175	Leu Ser Cys Thr Ser	180
Thr His Val Ser Glu	185	Leu Val Phe Phe Ile	190	Val Val Gly Val Ile	195
Thr Met Leu Ser Ser	200	Ile Ser Ile Val Ile	205	Ser Tyr Ala Leu Ile	210
Leu Ser Asn Ile Leu	215	Cys Ile Pro Ser Ala	220	Glu Gly Arg Ser Lys	225
Ala Phe Ser Thr Trp	230	Gly Ser His Ile Ile	235	Ala Val Ala Leu Phe	240
Phe Gly Ser Gly Thr	245	Phe Thr Tyr Leu Thr	250	Thr Ser Phe Pro Gly	255
Ser Met Asn His Gly	260	Arg Phe Ala Ser Val	265	Phe Tyr Thr Asn Val	270
Val Pro Met Leu Asn		Pro Ser Ile Tyr Ser		Leu Arg Asn Lys Asp	

275 280 285  
 Asp Lys Leu Ala Leu Gly Lys Thr Leu Lys Arg Val Leu Phe  
 290 295

<210> 36  
 <211> 307  
 <212> PRT  
 <213> Homo sapiens

<220>  
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 <223> Incyte ID No: 7472011CD1

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 Gly Leu Ser Gln Thr Arg Glu Leu Gln Arg Phe Leu Phe Leu Met  
 20 25 30  
 Phe Leu Phe Val Tyr Ile Thr Thr Val Met Gly Asn Ile Leu Ile  
 35 40 45  
 Ile Ile Thr Val Thr Ser Asp Ser Gln Leu His Thr Pro Met Tyr  
 50 55 60  
 Phe Leu Leu Arg Asn Leu Ala Val Leu Asp Leu Cys Phe Ser Ser  
 65 70 75  
 Val Thr Ala Pro Lys Met Leu Val Asp Leu Leu Ser Glu Lys Lys  
 80 85 90  
 Thr Ile Ser Tyr Gln Gly Cys Met Gly Gln Ile Phe Phe Phe His  
 95 100 105  
 Phe Leu Gly Gly Ala Met Val Phe Phe Leu Ser Val Met Ala Phe  
 110 115 120  
 Asp Arg Leu Ile Ala Ile Ser Arg Pro Leu Arg Tyr Val Thr Val  
 125 130 135  
 Met Asn Thr Gln Leu Trp Val Gly Leu Val Val Ala Thr Trp Val  
 140 145 150  
 Gly Gly Phe Val His Ser Ile Val Gln Leu Ala Leu Met Leu Pro  
 155 160 165  
 Leu Pro Phe Cys Gly Pro Asn Ile Leu Asp Asn Phe Tyr Cys Asp  
 170 175 180  
 Val Pro Gln Val Leu Arg Leu Ala Cys Thr Asp Thr Ser Leu Leu  
 185 190 195  
 Glu Phe Leu Lys Ile Ser Asn Ser Gly Leu Leu Asp Val Val Trp  
 200 205 210  
 Phe Phe Leu Leu Leu Met Ser Tyr Leu Phe Ile Leu Val Met Leu  
 215 220 225  
 Arg Ser His Pro Gly Glu Ala Arg Arg Lys Ala Ala Ser Thr Cys  
 230 235 240  
 Thr Thr His Ile Ile Val Val Ser Met Ile Phe Val Pro Ser Ile  
 245 250 255  
 Tyr Leu Tyr Ala Arg Pro Phe Thr Pro Phe Pro Met Asp Lys Leu  
 260 265 270  
 Val Ser Ile Gly His Thr Val Met Thr Pro Met Leu Asn Pro Met  
 275 280 285  
 Ile Tyr Thr Leu Arg Asn Gln Asp Met Gln Ala Ala Val Arg Arg  
 290 295 300  
 Leu Gly Arg His Arg Leu Val  
 305

<210> 37  
 <211> 314  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7472012CD1

<400> 37



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Gly	Ile	Ser	Thr	His	Pro	Glu	Glu	Gln	Ile	Pro	Leu	Phe	Leu	Val
				20					25					30
Phe	Ser	Leu	Met	Tyr	Ala	Ile	Asn	Ile	Ser	Gly	Asn	Leu	Ala	Ile
				35					40					45
Ile	Thr	Leu	Ile	Leu	Ser	Ala	Pro	Arg	Leu	His	Ile	Pro	Met	Tyr
				50					55					60
Ile	Phe	Leu	Ser	Asn	Leu	Ala	Leu	Thr	Asp	Ile	Cys	Phe	Thr	Ser
				65					70					75
Thr	Thr	Val	Pro	Lys	Met	Leu	Gln	Ile	Ile	Phe	Ser	Pro	Thr	Lys
				80					85					90
Val	Ile	Ser	Tyr	Thr	Gly	Cys	Leu	Ala	Gln	Thr	Tyr	Phe	Phe	Ile
				95					100					105
Cys	Phe	Ala	Val	Met	Glu	Asn	Phe	Ile	Leu	Ala	Val	Met	Ala	Tyr
				110					115					120
Asp	Arg	Tyr	Ile	Ala	Ile	Cys	His	Pro	Phe	His	Tyr	Thr	Met	Ile
				125					130					135
Leu	Thr	Arg	Met	Leu	Cys	Val	Lys	Met	Val	Val	Met	Cys	His	Ala
				140					145					150
Leu	Ser	His	Leu	His	Ala	Met	Leu	His	Thr	Phe	Leu	Ile	Gly	Gln
				155					160					165
Leu	Ile	Phe	Cys	Ala	Asp	Asn	Arg	Ile	Pro	His	Phe	Phe	Cys	Asp
				170					175					180
Leu	Tyr	Ala	Leu	Met	Lys	Ile	Ser	Cys	Thr	Ser	Thr	Tyr	Leu	Asn
				185					190					195
Thr	Leu	Met	Ile	His	Thr	Glu	Gly	Ala	Val	Val	Ile	Ser	Gly	Ala
				200					205					210
Leu	Ala	Phe	Ile	Thr	Ala	Ser	Tyr	Ala	Cys	Ile	Ile	Leu	Val	Val
				215					220					225
Leu	Arg	Ile	Pro	Ser	Ala	Lys	Gly	Arg	Trp	Lys	Thr	Phe	Ser	Thr
				230					235					240
Cys	Gly	Ser	His	Leu	Thr	Val	Val	Ala	Ile	Phe	Tyr	Gly	Thr	Leu
				245					250					255
Ser	Trp	Val	Tyr	Phe	Arg	Pro	Leu	Ser	Ser	Tyr	Ser	Val	Thr	Lys
				260					265					270
Gly	Arg	Ile	Ile	Thr	Val	Val	Tyr	Thr	Val	Val	Thr	Pro	Met	Leu
				275					280					285
Asn	Pro	Phe	Ile	Tyr	Ser	Leu	Arg	Asn	Gly	Asp	Val	Lys	Gly	Gly
				290					295					300
Phe	Met	Lys	Trp	Met	Ser	Arg	Met	Gln	Thr	Phe	Phe	Phe	Arg	
				305					310					

&lt;210&gt; 38

&lt;211&gt; 310

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472014CD1

&lt;400&gt; 38

Met	Gly	Arg	Asn	Asn	Leu	Thr	Arg	Pro	Ser	Glu	Phe	Ile	Leu	Leu
1				5					10					15
Gly	Leu	Ser	Ser	Arg	Pro	Glu	Asp	Gln	Lys	Pro	Leu	Phe	Ala	Val
				20					25					30
Phe	Leu	Pro	Ile	Tyr	Leu	Ile	Thr	Val	Ile	Gly	Asn	Leu	Leu	Ile
				35					40					45
Ile	Leu	Ala	Ile	Arg	Ser	Asp	Thr	Arg	Leu	Gln	Thr	Pro	Met	Tyr
				50					55					60
Phe	Phe	Leu	Ser	Ile	Leu	Ser	Phe	Val	Asp	Ile	Cys	Tyr	Val	Thr
				65					70					75
Val	Ile	Ile	Pro	Lys	Met	Leu	Val	Asn	Phe	Leu	Ser	Glu	Thr	Lys
				80					85					90
Thr	Ile	Ser	Tyr	Gly	Glu	Cys	Leu	Thr	Gln	Met	Tyr	Phe	Phe	Leu
				95					100					105

Ala	Phe	Gly	Asn	Thr	Asp	Ser	Tyr	Leu	Leu	Ala	Ala	Met	Ala	Ile	
				110					115						120
Asp	Arg	Tyr	Val	Ala	Ile	Cys	Asn	Pro	Phe	His	Tyr	Ile	Thr	Ile	
				125					130						135
Met	Ser	His	Arg	Cys	Cys	Val	Leu	Leu	Leu	Val	Leu	Ser	Phe	Cys	
				140					145						150
Ile	Pro	His	Phe	His	Ser	Leu	Leu	His	Ile	Leu	Leu	Thr	Asn	Gln	
				155					160						165
Leu	Ile	Phe	Cys	Ala	Ser	Asn	Val	Ile	His	His	Phe	Phe	Cys	Asp	
				170					175						180
Asp	Gln	Pro	Val	Leu	Lys	Leu	Ser	Cys	Ser	Ser	His	Phe	Val	Lys	
				185					190						195
Glu	Ile	Thr	Val	Met	Thr	Glu	Gly	Leu	Ala	Val	Ile	Met	Thr	Pro	
				200					205						210
Phe	Ser	Cys	Ile	Ile	Ile	Ser	Tyr	Leu	Arg	Ile	Leu	Ile	Thr	Val	
				215					220						225
Leu	Lys	Ile	Pro	Ser	Ala	Ala	Gly	Lys	Arg	Lys	Ala	Phe	Ser	Thr	
				230					235						240
Cys	Gly	Ser	His	Leu	Thr	Val	Val	Thr	Leu	Phe	Tyr	Gly	Ser	Ile	
				245					250						255
Ser	Tyr	Val	Tyr	Phe	Gln	Pro	Leu	Ser	Asn	Tyr	Thr	Val	Lys	Asp	
				260					265						270
Gln	Ile	Ala	Thr	Ile	Ile	Tyr	Thr	Val	Leu	Thr	Pro	Met	Leu	Asn	
				275					280						285
Pro	Phe	Ile	Tyr	Ser	Leu	Arg	Asn	Lys	Asp	Met	Lys	Gln	Gly	Leu	
				290					295						300
Ala	Lys	Leu	Met	His	Arg	Met	Lys	Cys	Gln						
				305					310						

&lt;210&gt; 39

&lt;211&gt; 359

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472020CD1

&lt;400&gt; 39

Met	Phe	Lys	Ala	Ile	Leu	Gly	His	Val	Trp	Pro	Lys	Asp	His	Gly	
1				5					10						15
Leu	Asp	Lys	Leu	Val	Val	Arg	Cys	Pro	Arg	His	Thr	Glu	Pro	Trp	
				20					25						30
Asn	Leu	Thr	Gly	Ile	Ser	Glu	Phe	Leu	Leu	Leu	Gly	Leu	Ser	Glu	
				35					40						45
Asp	Pro	Glu	Leu	Gln	Pro	Val	Leu	Pro	Gly	Leu	Ser	Leu	Ser	Met	
				50					55						60
Tyr	Leu	Val	Thr	Val	Leu	Arg	Asn	Leu	Leu	Ile	Ile	Leu	Ala	Val	
				65					70						75
Ser	Ser	Asp	Ser	His	Leu	His	Thr	Pro	Met	Cys	Phe	Phe	Leu	Ser	
				80					85						90
Asn	Leu	Cys	Trp	Ala	Asp	Ile	Gly	Phe	Thr	Ser	Ala	Met	Val	Pro	
				95					100						105
Lys	Met	Ile	Val	Asp	Met	Gln	Ser	His	Ser	Arg	Val	Ile	Ser	Tyr	
				110					115						120
Ala	Gly	Cys	Leu	Thr	Gln	Met	Ser	Phe	Phe	Val	Leu	Phe	Ala	Cys	
				125					130						135
Ile	Glu	Asp	Met	Leu	Leu	Thr	Val	Met	Ala	Tyr	Asp	Arg	Phe	Val	
				140					145						150
Ala	Ile	Cys	His	Pro	Leu	His	Tyr	Pro	Val	Ile	Met	Asn	Pro	His	
				155					160						165
Leu	Gly	Val	Phe	Leu	Val	Leu	Val	Ser	Phe	Phe	Leu	Ser	Leu	Leu	
				170					175						180
Asp	Ser	Gln	Leu	His	Ser	Trp	Ile	Val	Leu	Gln	Phe	Thr	Phe	Phe	
				185					190						195
Lys	Asn	Val	Glu	Ile	Ser	Asn	Phe	Val	Cys	Asp	Pro	Ser	Gln	Leu	
				200					205						210

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Leu Asn Leu Ala Cys Ser Asp Ser Val Ile Asn Ser Ile Phe Ile
      215      220
Tyr Leu Asp Ser Ile Met Phe Gly Phe Leu Pro Ile Ser Gly Ile
      230      235      240
Leu Leu Ser Tyr Ala Asn Asn Val Pro Ser Ile Leu Arg Ile Ser
      245      250      255
Ser Ser Asp Arg Lys Ser Lys Ala Phe Ser Thr Cys Gly Ser His
      260      265      270
Leu Ala Val Val Cys Leu Phe Tyr Gly Thr Gly Ile Gly Val Tyr
      275      280      285
Leu Thr Ser Ala Val Ser Pro Pro Pro Arg Asn Gly Val Val Ala
      290      295      300
Ser Val Met Tyr Ala Val Val Thr Pro Met Leu Asn Pro Phe Ile
      305      310      315
Tyr Ser Leu Arg Asn Arg Asp Ile Gln Ser Ala Leu Trp Arg Leu
      320      325      330
Arg Ser Arg Thr Val Glu Ser His Asp Leu Leu Ser Gln Asp Leu
      335      340      345
Leu His Pro Phe Ser Cys Val Gly Glu Lys Gly Gln Pro His
      350      355

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&lt;210&gt; 40

&lt;211&gt; 936

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 104941CB1

&lt;400&gt; 40

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gtggggaatg tgctcatcat cccggccatc tactctgacc ccaggctcca caccctatg 180
tacttttttc tcagcaactt gtctttcatg gatattctgt tcacaacagt catagtgcct 240
aagatgctgg tgaattttct atcagagaca aaggttatct cctatgtggg ctgcttgccc 300
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ggtttgaaga aattacagga cagaatttac cggtaa 936

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&lt;210&gt; 41

&lt;211&gt; 3365

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1499408CB1

&lt;400&gt; 41

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ctgcgcgagc tggggccgga cggacgcagc atcccgtggg ggccggctgga gcgcgcggac 180
gccgtggacc tcgcggagca gctggcccag ttctacggcc cggagcctgc cctggagggtg 240
gcccgaaga cctcaagag ggcggacgcg cgcgacgtgg cggcgacgct ccaggagcgg 300
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gaggcgctgg ggcccgcgga agagcctgag ccggggcgcg cggggcgctc ggacacgcac 540

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<210> 42
<211> 1325
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3168839CB1

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tgggtctacag cttggtgctg gctgcccggc tccccctcaa cgcgctagcc ctctgggtct 180
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gcgacctgct cttcaccctc tegctgcccg ttctgtctct ctactacgca ctgcaccact 300
ggccttccc cgacctcctg tgccagacga cgggcgcctat ctccagatg aacatgtacg 360
gcagctgat cttctgatg ctcacacacg tggaccgcta cgcgccatc gtgcaccgc 420
tgcgactgcg ccacctgcgg cgccccgcg tgggcgggct gctctgcctg ggctgtggg 480

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cgctcatcct ggtgtttgcc gtgcccgcgc cccgcgtgca caggccctcg cgttgccgct 540
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&lt;210&gt; 43

&lt;211&gt; 2124

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3291235CB1

&lt;400&gt; 43

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&lt;210&gt; 44

&lt;211&gt; 942

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
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 <223> Incyte ID No: 7472001CB1

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<220>  
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 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7472004CB1

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 gccatgaggt ctgcaattaa catcctcctt gccagcctag cttttgcaga catgttgctt 240

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<210> 47  
 <211> 582  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7475687CT1

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gttgctactc cattactgaa cccctcctc tataactga ggaaccagga agtgaagtct 540
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<210> 48  
 <211> 519  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7483029CT1

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<400> 48
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attaatgaca tgatgatgaa ttttacaagt gtgctgctg          519

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<210> 49  
 <211> 663  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7477933CT1

<400> 49

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&lt;210&gt; 50

&lt;211&gt; 911

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7475164CT1

&lt;400&gt; 50

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&lt;210&gt; 51

&lt;211&gt; 332

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7473909CT1

&lt;400&gt; 51

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&lt;210&gt; 52

&lt;211&gt; 538

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7475252CT1

&lt;400&gt; 52



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<210> 53  
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 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7927572CT1

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<210> 54  
 <211> 291  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7481257CT1

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<210> 55  
 <211> 402  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7485790CT1

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<400> 55
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<210> 56  
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 <212> DNA  
 <213> Homo sapiens

<220>  
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&lt;223&gt; Incyte ID No: 7482993CT1

&lt;400&gt; 56

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&lt;210&gt; 57

&lt;211&gt; 1370

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2829053CB1

&lt;400&gt; 57

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&lt;210&gt; 58

&lt;211&gt; 1567

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

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&lt;223&gt; Incyte ID No: 3068234CB1

&lt;400&gt; 58

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&lt;210&gt; 59

&lt;211&gt; 1321

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5029478CB1

&lt;400&gt; 59

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&lt;210&gt; 60

&lt;211&gt; 1110

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5102576CB1

&lt;400&gt; 60

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&lt;210&gt; 61

&lt;211&gt; 1095

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2200534CB1

&lt;400&gt; 61

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&lt;210&gt; 62

&lt;211&gt; 1665

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

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&lt;223&gt; Incyte ID No: 3275821CB1

&lt;400&gt; 62

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<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 3744167CB1

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<211> 945
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
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<400> 64

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&lt;210&gt; 65

&lt;211&gt; 1098

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472008CB1

&lt;400&gt; 65

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

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&lt;223&gt; Incyte ID No: 7472013CB1

&lt;400&gt; 66

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cgagcagctc ccacctgtgg atcccacctc accatgggtg gtttctcta cggcaccatc 780
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gtaatgtata ctgccattac acctttggcc aacccatttg tgtatagcct ccacaataag 900
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<210> 67  
 <211> 1008  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7472015CB1

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tattggcaga aggaggtgcg actgcagctc taccacatgg ccctaggagt gaagaagggtg 900
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<210> 68  
 <211> 930  
 <212> DNA  
 <213> Homo sapiens

<220>  
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ggaaacctgc tcattgtcct agccatttgc tctgatgttc gcttccacaa ccccatgtat 180
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tgtatctggc ttattgctgg gtcttgggtg attggaaatg ccaatgccct cccccacact 480
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<210> 69  
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 <212> DNA  
 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472017CB1

&lt;400&gt; 69

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gttgcggtggc tgagtggagt gggaaacact cttatccagg gcactgtcac cctctggctt 300
cctcgctgtg gacaccgatt gctccaacat ttcttcttg catgtgtgga catccatgat 360
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atcacagctg tctacatcca gtccaacagt tcttatgccc atgctcatgg gaagttcatc 600
tccctcttct atacagttgt gaccccgacc ctcaatcctc tcatctacac actgaggaat 660
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&lt;210&gt; 70

&lt;211&gt; 1092

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472018CB1

&lt;400&gt; 70

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cagacacact ga 1092

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&lt;210&gt; 71

&lt;211&gt; 927

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472019CB1

&lt;400&gt; 71

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gggaatggat ttatgatctt tcttatccac tttagcccca acctccacac tccaatctac 180
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gctttgtgtg attgtttctc taacctccc tactctcttt atccccgat tttggctcaa 300
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&lt;210&gt; 72

&lt;211&gt; 1032

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472021CB1

&lt;400&gt; 72

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cgtaagcttc agatttttaca tgcattggta tttctgggtga catacctgct ggccttgaca 180
ggcaacctcc tcattatcac catcattacc gtggaccgtc gtctccattc ccccatgtat 240
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tcatttgcaa attcacttat gggcaacggt tacatttctc ttgttcagtg cattcttcag 360
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&lt;210&gt; 73

&lt;211&gt; 972

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7472009CB1

&lt;400&gt; 73

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ggcaacaccc tcaccattct cctcatctgc attgatcccc agcttcatac accaatgtat 180
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agaagagtgc tgaggagaga tgttatcacc cagtgcattc aacgactgca attgtgggtg 960
ccccgagtgt ag          972

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&lt;210&gt; 74

&lt;211&gt; 900

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<213> Homo sapiens

<220>  
<221> misc\_feature  
<223> Incyte ID No: 7472010CB1

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ctctgttatt cctgtgtgtt tcccccaaa atgtgtgaatg actttgtttc agaaagtatc 240  
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tgctatgtgt tggatatcaat ggccatgat cgctatgtgg ccacttgcaa cccctgctc 360  
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gggtttgctg gggccatggc ccacactgga agcatgctgc gactgacctt ctgtgattcc 480  
aacgtcattg accattatct gtgtgacgtt cccccctct tgcagctctc ctgcaccagc 540  
acccatgtca gtgagctggg atttttcatt gttgttggag taatcaccat gctatccagc 600  
ataagcatcg tcatctctta cgttttgata ctctccaaca tctctgtgat tcttctgca 660  
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agatttgctt cagtctttta caccaatgtg gttcccatgc ttaacccttc gatctacagt 840  
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<212> DNA  
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<220>  
<221> misc\_feature  
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ggaacatccc ttatcatcat cacagtgacc tctgattccc agctccacac acccatgtac 180  
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gttccccaa g tactgagact tgctgtcact gacacctcac tgcctggagt cctcaagate 600  
tccaacagt ggcgtctgga tgcgtctgg ttctctctc tctgatgtc ctacttatc 660  
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<211> 945  
<212> DNA  
<213> Homo sapiens

<220>  
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<210> 77  
 <211> 933  
 <212> DNA  
 <213> Homo sapiens

<220>  
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 <223> Incyte ID No: 7472014CB1

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 <211> 1080  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7472020CB1

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ctgggactct cagaggatcc agaactgcag ccgctctcc ctgggctgtc cctgtccatg 180
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